REMARKS

Applicants respectfully request the Examiner to reconsider the present application in view of the foregoing amendments to the claims.

Status of the Claims

In the present Reply, claims 1, 2, 4, 8, 10 and 15 have been amended. Claims 13-14 and 18-20 were previously canceled without prejudice or disclaimer of the subject matter contained therein. Claims 11-12 and 16-17 are canceled herein without prejudice or disclaimer of the subject matter contained therein. Claims 4 and 8 are allowable if properly rewritten (see paragraph 8, page 7 of the Office Action). The amendment to claims 4, 8 and 15 are clearly non-narrowing claim amendments. Thus, claims 1-10, 15 and 21 are pending in the present application.

No new matter has been added by way of these amendments, because each amendment is supported by the present specification. For example, claims 4 and 8 have been merely amended into independent form by incorporating the subject matter of the base claim (claim 1) and any intervening claim (*i.e.*, claim 6) (see paragraph 8 of the Office Action). Also, the amendments to claims 1, 2 and 10 merely delete subject matter. Thus, no new matter has been added.

Based upon the above considerations, entry of the present amendment is respectfully requested.

In view of the following remarks, Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

Paragraphs 1 and 4 of the Office Action

Applicants acknowledge the withdrawn rejections as outlined in paragraphs 1 and 4 (pages 2 and 4, respectively) of the Office Action.

Issues Under 35 U.S.C. § 112, First Paragraph

Claims 11, 12, 15-17 and 21 stand rejected under 35 U.S.C. 112, first paragraph, for asserted failure to comply with the enablement requirement (see paragraph 2 of this Office Action, especially the paragraph bridging pages 3-4, and paragraph 3 of the previous Office Action dated May 2, 2004). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Some rejections rendered moot; no *prima facie* case; enablement for other claims

Applicants first note that the rejection of claims 11, 12, 16 and 17 has been rendered moot with the cancellation of these claims.

With regard to claims 15 and 21, Applicants respectfully maintain their position that the burden of proving enablement has not shifted to Applicants since "the initial burden of establishing a *prima facie* basis

to deny patentability to a claimed invention on any ground is always upon the examiner." *Ex parte* Parks, 30 USPQ2d 1234, 1236 (citing In *re Oetiker*, 24 USPQ2d 1443 (Fed. Cir. 1992)); *see also In re Piasecki*, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984). The burden has not shifted to Applicants since the Examiner has not established a *prima facie* case of nonenablement because the Examiner has not provided "acceptable evidence of nonenablement". *See Utter v. Hiraga*, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988) (That some experimentation is necessary does not preclude enablement, however, unless the amount of experimentation is unduly extensive); *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Further, sufficient enablement exists as explained below.

With regard to claim 15, the Office Action focuses on the "how to use" requirement of 35 U.S.C. § 112, first paragraph and refers Applicants to M.P.E.P. § 2164.01 for support. However, this very same section of the M.P.E.P. states that "when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use." Applicants submit that is the case here, wherein pending claim 15 is given the presumption of enablement and instantly precludes a rejection for enablement. *See* M.P.E.P. § 2164.01, page 2100-187 (Latest Revision May 2004). Applicants further note that the previous paragraph of this part of the M.P.E.P. refers to a chimeric gene capable of being

expressed in any cyanobacterium as an example of use for a compound or composition claim. That paragraph is not applicable here. Withdrawal of the rejection of claim 15 is respectfully requested.

With regard to claim 21, Applicants respectfully submit that the Examiner has misquoted the scope of this claim in the sentence bridging pages 2-3 of the Office Action. Pending claim 21 is directed to treating types of senile dementia or cerebrovascular dementia, and not the scope as the Examiner is asserting. The Examiner's comments appear to be mainly directed to claim 16, which has been canceled herein. Thus, withdrawal of the rejection of claim 21 is respectfully requested.

Claim 21: enablement by the present specification and state of the art

With respect to any further issue regarding the sufficiency of disclosure of the inhibitors of acetylcholine esterase and the diseases or conditions recited in claim 21, Applicants respectfully request the Examiner to review the excerpt provided below since Applicants believe that this excerpt from a scientific article (from "Cholinesterase Inhibitors of Alzheimer's Disease," John C. Morris *et al.*, *Drugs*, Vol. 61(1), pp. 41-52 (2001)) sufficiently rebuts the Examiner's (non *prima facie*) rejection.

> … Alzheimer's disease (AD) is the most common age-related neurodegenerative disease and has become an urgent public health problem in most areas of the world. Substantial progress has been made in understanding the basic neurobiology of AD and, as a result, new drugs for its treatment have become available. Cholinesterase inhibitors (ChEIs), which

> increase the availability of acetylcholine in central synapses, have become the main approach to symptomatic treatment. ChEIs that have been approved or submitted to the US Food and Drug Administration (FDA) include tacrine, donepezil, metrifonate, rivastigmine and galantamine. In this review, the pharmacology and clinical experience to date is discussed together with their use and their potential benefits or disadvantages. ChEIs have a significant, although modest, effect on the cognitive status of patients with AD.
>
> In addition to their effect on cognition, ChEIs have a positive effect on mood and behavior. Uncertainty remains about the duration of the benefit because few studies of these compounds beyond one year have been published. Although ChEIs are generally well tolerated, all patients should be followed closely for possible adverse effects. There is no substantial difference in the effectiveness of the various ChEIs, however, they may have different safety profiles. The benefits of their use outweigh the risks and costs and, therefore, ChEIs should be considered as primary therapy for patients with mild to moderate AD.

The present invention has the same mechanism of action as donepezil.

Further, this same *Drugs* article by John C. Morris *et al.* at pages 45-46 states:

> … In November 1996, donepezil became the second drug to receive FDA approval for treatment of cognitive symptoms in patients with AD. Donepezil, a piperidine-based reversible ChEI (cholinesterase inhibitors), is highly selective for AchE (acetyl cholinesterase inhibitors) in the CNS. Its long terminal disposition half-life (70 hours) supports once-daily administration, and there is no requirement for dose modification in the elderly or in patients with renal or hepatic impairment.
>
> <u>The crucial evidence of efficacy of this compound came from a 24-week study in patients with mild to moderate AD.</u>
>
> This was a randomised, double-blind, multicentre, parallel group study of donepezil 5 or 10 mg/day versus placebo, with 150 patients per treatment group. The drug was administered for 24 weeks followed by a 6-week single-blind, placebo washout. Primary measures of efficacy were the ADAS-

> cognitive subscale and the Clinician Interview-Based Impression of Change, incorporating caregiver input (CIBIC-Plus). Secondary measures of efficacy included the Mini-Mental Status Examination (MMSE) and the Clinical Dementia Rating Sum-of-the-Boxes (CDR-SB).
>
> Cognitive function, as measured by the ADAS-cog, was significantly improved in the donepezil 5 and 10 mg/day groups compared with the placebo group at weeks 12, 18 and 24 (2.49-point improvement for the 5 mg/day group and 2.88 for the 10mg/day group). Clinician's global ratings on the CIBIC-Plus, CDR-SB and MMSE also improved in both the donepezil 5 and 10 mg/day groups relative to placebo.
>
> Donepezil was well tolerated over the course of the study, especially with dose titration (i.e. initiating donepezil at 5 mg/day and increasing to 10mg/day after at least 2 weeks). The 10 mg/daygroup had a statistically significantly higher frequency of diarrhoea and vomiting compared with the 5 mg/day and placebo groups. These adverse effects were generally of mild severity and brief duration and usually resolved despite continued treatment. No clinically significant effects on vital signs, haematology or clinical biochemistry tests were observed. Importantly, donepezil was not associated with the hepato toxicity observed with acridine-based ChEIs such as tacrine. Additional studies also support that donepezil 5 to 10 mg/day is a well tolerated and efficacious agent for treating the symptoms of patients with mild to moderately severe AD.

(Applicants emphasis added).

Applicants emphasis is added to the excerpt above, since other references are relevant to the present enablement issue.

With regard to the crucial evidence of efficacy of donepezil stemming from a 24-week study in patients having mild to moderate Alzheimer's Disease (the first underlined passage in the *Drugs* excerpt above), which concerns clinical efficacy of donepezil usefulness, Applicants respectfully refer the Examiner to reference a), which is hereby attached:

a) Rogers SL *et. al.*, "A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease: Donepezil Study Group," *Neurology*, Vol. 50, pp. 136-45 (1998).

With regard to the additional studies (the second underlined passage in the excerpt above) that support donepezil efficacy as treating mild to moderaly severe AD, Applicants respectfully refer the Examiner to reference a) above as well as the following reference b), also hereby attached:

b) Rogers SL *et. al.*, "Donepezil improves cognition and global function in Alzheimer disease-a 15-week, double-blind, placebo-controlled study: Donepezil Study Group., *Arch. Intern. Med.*, Vol. 158, pp. 1021-31 (1998).

Both of these scientific articles were published before the application of the present invention. Thus, though the Office Action states that the *Drugs* article cannot be used for show enablement (see page 3, lines 3-5 of the Office Action), Applicants note that the two other articles above do represent the state of the art at the time the present application was filed. Further, the *Drugs* article concerns references a) and b), as mentioned above, because the article concerns the state of the art as exemplified by references a) and b). Accordingly, consideration of all three articles is respectfully requested. Applicants provide the following summary of the two scientific articles a) and b) below.

Summary of Two References a) and b)

Donepezil, referred to in the literature, is a compound having the same mechanism of action as the compound of the present invention. The present invention is an inhibitor of acetylcholinesterase. Donepezil is also a ChEI and is a commercially available medicament for treating Alzheimer's Disease. Donepezil has very strong commercial sales world-wide. Thus, one of ordinary skilled in the art would understand and take it for granted that the instantly claimed compounds of the present application are efficacious for treating or improving senile dementia and cerebrovascular dementia based on the state of the art and Applicants' specification. Thus, Applicants respectfully submit that one of skill in the art would know how to make and use the present invention since the skilled artisan understands that the present invention acts like donepezil.

Accordingly, the rejection in paragraph 3 of the Office Action has been obviated. Reconsideration and withdrawal of this rejection are respectfully requested.

Issues Under 35 U.S.C. § 112, Second Paragraph

Claims 10, 12, 15, 16, 17 and 21 stand rejected under 35 U.S.C. § 112, second paragraph, for asserted reasons of indefiniteness (for the reasons stated in paragraphs 3, page 4 and paragraph 5, pages 5-6 of the Office Action). Applicants respectfully traverse.

First, claims 12, 16 and 17 have been canceled, rendering the rejection of these claims moot.

Second, with regard to claim 21, Applicants herein incorporate the remarks above regarding the enablement rejection. Further, the scope of diseases or disorders as recited in claim 21 does "alter over time" as the Examiner is asserting in the Office Action. Thus, withdrawal of this rejection is respectfully requested.

With regard to claim 10, Applicants respectfully refer the Examiner to the scope of the claim as presented. The 13th to 18th species have been canceled, rendering this rejection moot. Withdrawal of this rejection is respectfully requested.

With regard to claim 15, claim 11 has been canceled. Thus, this rejection is rendered moot since claim 15 is not duplicative of any other pending claim.

Based on the above, withdrawal of this rejection is respectfully requested.

Issues Under 35 U.S.C. § 102(b)

Claims 1-3, 5-7, 9, 11, 12, 15-17 and 21 stand rejected under 35 U.S.C. § 102(b) as being anticipated by JP 09-268176 (hereinafter "JP '176") (see paragraph 6, page 6 of the Office Action). Applicants respectfully traverse since JP '176 fails to disclose all claimed features.

Applicants respectfully refer the Examiner to the scope of the claims as presented. JP '176 fails to disclose the presently claimed compounds, especially in consideration of the claimed R^5 groups (R^5 refers to R^1, which refers to formula (I)). Because "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference," the cited JP '176 reference cannot be a basis for a rejection under § 102(b). *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Thus, because of the lack of disclosure of all features as instantly claimed, the rejection in view of JP '176 is overcome. Reconsideration and withdrawal are respectfully requested.

Issues Under 35 U.S.C. § 103(a)

Claims 1-3, 5-7, 9, 11, 12, 15-17 and 21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable JP '176 (see paragraphs 7 of the Office Action). Applicants respectfully traverse, and reconsideration and withdrawal of this rejection are respectfully requested.

Applicants respectfully refer the Examiner to the scope of the claims as presented. JP '176 fails to disclose the presently claimed compounds, especially in consideration of the claimed R^5 groups (R^5 refers to R^1, which refers to formula (I)). Because a *prima facie* case of obviousness requires disclosure of all claimed features, this

rejection has been overcome. *See In re Vaeck*, 947 F.2d, 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Applicants also submit that one of ordinary skill in the art would not be motivated or reasonably expect to be successful in achieving the present invention by reading JP '176 since this reference does not disclose or suggest modifying the group corresponding to the present R^5 group to obtain the present invention.

Thus, Applicants submit that this rejection has been overcome. Reconsideration and withdrawal thereof are respectfully requested.

Paragraph 9 of the Office Action

With regard to paragraph 9 of the Office Action, Applicants submit that the instant claims do not overlap with the cited Published Patent Application No. 20040048893. Applicants respectfully refer the Examiner to the scope of R^5 of the present invention. Interference proceedings would not be necessary. Also, a certified English translation of the priority document for this application is enclosed (JP 11-247115, filed September 1, 1999).

Conclusion

A full and complete response has been made to all issues as cited in the Office Action. Applicants have taken substantial steps in efforts to advance prosecution of the present application. Thus,

Applicants respectfully request that a timely Notice of Allowance issue for the present case.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Eugene T. Perez (Reg. No. 48,501) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Marc S. Weiner, #32,181

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

MSW/ETP
0425-0877P

Attachments:
-Rogers SL *et. al.*, "A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease: Donepezil Study Group," *Neurology*, Vol. 50, pp. 136-45 (1998)
-Rogers SL *et. al.*, "Donepezil improves cognition and global function in Alzheimer disease-a 15-week, double-blind, placebo-controlled study: Donepezil Study Group., *Arch. Intern. Med.*, Vol. 158, pp. 1021-31 (1998)
-Certified English translation of JP 11-247115

peroxisomal function in ischemia-reperfusion injury of rat kidney. Biochim Biophys Acta 1993;1182:291–298.
24. Cheney P. Early management and physiologic changes in crush syndrome. Crit Care Nurs Q 1994;17:62–73.
25. Martinez M. Polyunsaturated fatty acid changes suggesting a new enzymatic defect in Zellweger syndrome. Lipids 1989;24: 261–265.
26. Thomas DW, van Kuijk FJGM, Stephens RJ. Quantitative determination of hydroxy fatty acids as an indicator of *in vivo* lipid peroxidation: oxidation products of arachidonic and docosapentaenoic acids in rat liver after exposure to carbon tetrachloride. Anal Biochem 1992;206:353–358.
27. Wang T, Yu W, Powell WS. Formation of monohydroxy derivatives of arachidonic acid, linoleic acid, and oleic acid during oxidation of low density lipoprotein by copper ions and endothelial cells. J Lipid Res 1992;33:527–537.
28. Nikkari T, Malo-Ranta U, Hiltunen T, Jaakkola O, Vlä-Herttuala S. Monitoring of lipoprotein oxidation by gas chromatographic analysis of hydroxy fatty acids. J Lipid Res 1995; 36:200–207.

A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease

S.L. Rogers, PhD; M.R. Farlow, MD; R.S. Doody, MD, PhD; R. Mohs, PhD; L.T. Friedhoff, MD, PhD; and the Donepezil Study Group*

Article abstract—The efficacy and safety of donepezil as a treatment for patients with mild to moderate Alzheimer's disease (AD) was investigated in a multicenter, double-blind study. Patients were randomly assigned to treatment with placebo (n = 162), 5 mg/d donepezil (n = 154), or 10 mg/d donepezil (n = 157) for 24 weeks followed by a 6-week, single-blind placebo washout. The primary efficacy measures were the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview Based Assessment of Change-Plus (CIBIC plus), with the Mini-Mental State Examination (MMSE), Clinical Dementia Rating Scale-Sum of the Boxes (CDR-SB), and patient rated Quality of Life (QoL) used as secondary measures. Cognitive function, as measured by the ADAS-cog, was significantly improved in the 5- and 10-mg/d donepezil groups as compared with the placebo group at weeks 12, 18, and 24. Clinician's global ratings on the CIBIC plus also improved in both the 5- and 10-mg/d donepezil groups relative to placebo. At the end of the 6-week placebo washout phase, ADAS-cog scores and CIBIC plus ratings were not significantly different for the three groups. Significant treatment benefits were also observed consistently in both the 5- and 10-mg/d groups on the MMSE and the CDR-SB, but there was no consistent effect on the patient-rated QoL. Cholinergic side effects (primarily diarrhea, nausea, and vomiting) were reported more often in the 10-mg/d group than either the 5-mg/d or placebo groups. Side effects were transient and generally mild in severity. These data indicate that donepezil is a well-tolerated drug that improves cognition and global function in patients with mild to moderate AD.

NEUROLOGY 1998;50:136–145

Alzheimer's disease (AD) is characterized by deficits in memory and cognition that are associated with significant losses of presynaptic cholinergic function in the brain, particularly the nucleus basalis.[1-3] It has been hypothesized that cholinergic agents, either cholinesterase (ChE) inhibitors or cholinergic agonists, might improve these clinical symptoms.[4]

ChE inhibitors act by blocking acetylcholinesterase (AChE) and butylcholinesterase (BuChE), enzymes that normally hydrolyze acetylcholine. However, many ChE inhibitors lack selectivity for AChE in the CNS and consequently may have to be given at elevated doses to elicit a clinically important effect. This can result in peripheral ChE inhibition and unacceptable side effects such as dyspepsia, nausea, vomiting, and diarrhea.[5] Some ChE inhibitors such as tacrine and velnacrine also cause hepatotoxicity in many patients.[6-9] Hence, the clinical utility of some compounds in the treatment of AD has been limited by their side effects.

To date, two ChE inhibitors have been approved by the U.S. Food and Drug Administration (FDA) to treat AD: tacrine, an acridine, and donepezil hydrochloride, a piperidine. However, many other agents are used experimentally, some of which are currently undergoing systematic clinical evaluation.

*See the Appendix on page 144 for a listing of the members of the Donepezil Study Group.

From Eisai Inc. (Drs. Rogers and Friedhoff), Teaneck, NJ; the Indiana University School of Medicine (Dr. Farlow), Indianapolis, IN; Baylor College of Medicine (Dr. Doody), Houston, TX; and the Mount Sinai Medical Center (Dr. Mohs), New York, NY.

Supported by Eisai Inc., Teaneck NJ, U.S.A. and Eisai Co. Ltd., Tokyo, Japan.

Received March 12, 1997. Accepted in final form August 20, 1997.

Address correspondence and reprint requests to Dr. L. T. Friedhoff, Eisai Inc., Glenpointe Centre West, 500 Frank W. Burr Blvd., Teaneck, NJ 07666-6741.

Donepezil is an AChE inhibitor that is chemically distinct from other drugs studied for the treatment of AD. In preclinical investigations, donepezil has been shown to have greater specificity for AChE than either tacrine or physostigmine and a longer duration of action than either of these drugs.[10] The AChE:BuChE binding ratio of donepezil is the highest available in this class of agents, indicating that donepezil possesses high central versus peripheral cholinomimetic specificity[10] and, thus, a favorable efficacy to side-effect ratio and therapeutic margin. Indeed, in phase I and II studies of donepezil, no evidence of clinically significant adverse events or hepatotoxicity were observed.[11]

The present phase III study was undertaken to further evaluate the efficacy and safety of donepezil at dosage levels of 5 and 10 mg/d versus placebo in patients with mild to moderate AD.

Methods. *Patient population.* Patients eligible for this study had a diagnosis of uncomplicated AD. These men and women of any race aged 50 years or older showed no evidence of insulin-dependent diabetes mellitus or other endocrine disorders; asthma or obstructive pulmonary disease; or clinically significant uncontrolled gastrointestinal, hepatic, or cardiovascular diseases. The diagnosis of probable AD was made according to criteria outlined by the National Institute of Neurological and Communicative Disorders and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), with patients also fitting DSM-III-R illness categories of 290.00 or 290.10, with no clinical or laboratory evidence of a cause other than AD for their dementia.[12,13] Patients had scores on the Mini-Mental State Examination (MMSE) of 10 to 26, and a Clinical Dementia Rating (CDR) score of 1 (mild dementia) or 2 (moderate dementia) at both screening and baseline.[14,15] Patients who were known to be hypersensitive to ChE inhibitors or had been taking tacrine and/or other investigational medications within 1 month of baseline were excluded. Concomitant medications such as anticholinergics, anticonvulsants, antidepressants, and antipsychotics were not allowed during the course of this study. Drugs with CNS activity were either prohibited or partially restricted. All other medications were permitted. Patients were required to have a reliable caregiver. Written informed consent was obtained from both the patient and from their caregiver.

Study design. This was a 24-week, randomized, double-blind, placebo-controlled study, ending with a single-blind placebo washout phase of 6 weeks. Treatment group status was assigned by a computerized randomization schedule. The trial was conducted at 20 investigational sites in the United States with 473 patients being enrolled into three approximately equal groups: placebo (n = 162), donepezil 5 mg/d (n = 154), and donepezil 10 mg/d (n = 157). Patients received their treatment, a single dose, once each evening. For the maximum dosage group (10 mg/d donepezil), a blinded forced titration scheme was used in which subjects received 5 mg/d donepezil for the first week and then 10 mg/d for the remainder of the study.

Measures of clinical outcome were assessed at baseline and at 6-week intervals. Protocol-specified primary outcome measures were the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-cog) and a Clinician's Interview-Based Impression of Change scale that included caregiver supplied information (CIBIC plus).[16,17] Protocol-specified secondary outcome measures were the MMSE, patient-rated quality of life (QoL) scale, and the Sum of the Boxes of the CDR scale (CDR-SB).[14,18,19] Donepezil concentrations in plasma were measured,[20] and an analysis quantifying inhibition of RBC AChE activity[21] was performed on blood samples collected from all patients at their baseline and at 6-, 12-, 18-, 24-, and 30-week visits. Patients who withdrew early were encouraged to return for the 24- and 30-week evaluations for retrieved dropout analyses. Safety was assessed at 6-week intervals by physical examinations, clinical laboratory tests, adverse event monitoring, and by evaluation of the general health and well-being of the patient. All patients completing the double-blind phase of this study were eligible to receive donepezil during a subsequent open-label study.

Measures of efficacy. The ADAS-cog is a sensitive and reliable neuropsychological test consisting of an 11-item scale used to assess the severity of selected areas of cognitive impairment (memory, language, orientation, reason, and praxis). Scores range from 0 to 70 with lower scores indicating lesser severity. Its use in assessing and following changes in cognitive function in patients with AD has been extensively validated.[22] On average, untreated patients with moderately severe AD show an increase (cognitive decline) of approximately 7 to 11 points per year.[23,24] However, the ADAS-cog is not uniformly sensitive over the course of the disease. Thus, scores for patients with very mild or very severe disease may increase only 0 to 5 points per year.

The CIBIC plus is not an instrument but an interview technique used by a clinician who is barred from knowledge of all psychometric test scores, laboratory values, and adverse event reports obtained as part of the protocol. The format used for this trial (CIBIC plus) was developed from the Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC).[17] It provides a global rating score that reflects patient function in four areas: general, cognitive, behavior, and activities of daily living. It is derived through independent and comprehensive interviews with both patient and caregiver. Clinical trials of antidementia agents have used a variety of CIBIC formats, each differing in depth and structure. The clinician first assesses disease severity at baseline. Using the results from baseline for reference, the clinician then interviews the patient and caregiver at specified times during the study to obtain an impression of change. The order of interviewees (patient and caregiver) was randomized at each visit. After the interview, a seven-point Likert-type scale is used for scoring, where 1 is marked improvement, 4 is no change, and 7 represents marked worsening.

The MMSE is a widely used brief test for evaluating the cognitive state of patients. The QoL is a patient-rated seven-item scale that evaluates the patient's feeling of well-being. The basic domains examined are relationships, eating and sleeping, and social and leisure activity. The CDR-SB sums the ratings in each of six domains ("boxes") of the CDR to provide a consensus-based global clinical measure (i.e., the Sum of the Boxes). The domains include memory, orientation, judgment and problem solving, com-

munity affairs, home and hobbies, and personal care. The ratings for each domain are agreed on by the members of the patient's assessment team, except the clinician conducting the CIBIC plus, after review and consideration of the results from all neuropsychological tests conducted during clinic visits.

Statistical assessments. Sample sizes for this study were selected based on a review of clinical studies of other ChE inhibitors[6,9] and the results of earlier phase II studies of donepezil. The analyses for efficacy in this study was performed on two patient populations: the fully evaluable and intent to treat (ITT). The fully evaluable population was defined as all patients who completed 24 weeks of double-blind treatment with at least 80% compliance of study medication at week 24 and had at least two other visits during the double-blind phase with no significant protocol violations. Intent-to-treat analysis included all subjects who were randomized to treatment, received at least one dose of the study drug, provided complete baseline data, plus a minimum of one post-baseline data point. The efficacy conclusions were based on the results at each patient's last assessment during double-blind therapy, defined as study endpoint (i.e., last observation carried forward (LOCF) as outlined by the FDA).[25] Both the 5- and 10-mg/d-donepezil treatment groups were compared against placebo.

For continuous efficacy variables (ADAS-cog, MMSE, CDR-SB, and QoL), a linear model was used to construct ANCOVA to compare the treatment groups: changes from baseline score measured against each subsequent visit (weeks 6, 12, 18, 24, and 30) to endpoint. The models contained factors for baseline score, treatment effect, center effect, treatment-by-center interaction, and random error. The overall treatment effects (difference in efficacy between the three treatment groups) were analyzed using type III sums of squares performed to determine statistical significance. In cases where differences existed, pairwise comparisons between active treatment and placebo were undertaken using Fisher's two-tailed least significant difference procedure.

The categorical efficacy variable, the CIBIC plus, was analyzed using the Cochran-Mantel-Haenszel test with RIDITS as the score option and included adjustments for center differences.

Comparability of the three groups for quantitative differences in continuous demographic variables (e.g., age, weight, height) was assessed using ANOVA models with factors for treatment and center. Comparability of the groups with regard to categorical variables such as race and sex was assessed using the Cochran-Mantel-Haenszel procedure with centers as strata.

Intragroup changes in vital signs (baseline versus endpoint) were analyzed using paired t-tests, and between treatment differences were detected by ANOVA. The analysis of adverse events was confined to treatment-emergent signs and symptoms (TESS) that began during or after administration of the first dose of study medication or became more severe during treatment. Events, recorded using investigator terminology, were grouped and coded into common terms using a modified COSTART dictionary.[26] Investigator assessment of relationship to treatment for all adverse events, serious and nonserious, was conducted under blinded conditions.

Table 1 *Summary of demographic characteristics of patients randomized to study treatments*

Characteristics	Treatment groups		
	Placebo (n = 162)	Donepezil 5 mg/d (n = 154)	Donepezil 10 mg/d (n = 157)
Age* (y)	72.6 ± 0.6	72.9 ± 0.6	74.6 ± 0.6†
(range)	(56–88)	(51–86)	(53–94)
Sex			
Male (%)	63 (39)	57 (37)	60 (38)
Female (%)	99 (61)	97 (63)	97 (62)
Race			
White (%)	153 (94)	146 (95)	150 (96)
African-American (%)	6 (4)	5 (3)	3 (2)
Other (%)	3 (2)	3 (2)	4 (3)
Screening CDR			
0.5 (%)	0	1 (1)‡	0
1.0 (%)	121 (75)	114 (74)	119 (76)
2.0 (%)	41 (25)	39 (25)	37 (24)
Screening MMSE*	19.2 ± 0.4	19.0 ± 0.4	18.9 ± 0.4

* Values are means ± SEM.

† The difference in mean age between the 10 mg/d donepezil treatment group and the placebo group was significant (p = 0.03).

‡ Patient was subsequently excluded as a protocol violation.

The incidences of TESS and treatment-emergent abnormal laboratory values (TEAVs) (i.e., newly occurring or clinically significant exacerbations of pre-existing abnormalities) were compared across treatment groups using Fisher's exact test.

All statistical analyses were performed using SAS version 6 (SAS Institute, Cary, NC). All hypothesis tests were two-sided, with analyses being significant if a $\leq$0.05 level was achieved.

Results. *Demographic characteristics.* Patient demographic characteristics did not differ between treatment groups, except for age (table 1). The mean age of the donepezil 10-mg/d group was 2 years older than the mean for the placebo group (p = 0.03). Other patient characteristics such as weight, height, and caffeine and alcohol use were similar between the groups (data not shown).

Efficacy assessment. As a consequence of the low discontinuation rate recorded in this trial, evaluable patient population and intent-to-treat (ITT) analyses gave results that were essentially the same. Further discussion of these results will report the more conservative ITT analyses.

Primary efficacy parameters: ADAS-cog. As indicated in figure 1, the mean ADAS-cog score for the placebo group actually improved after 6 weeks versus baseline but steadily worsened at each 6-week interval thereafter. This temporary improvement in placebo is consistent with the observation in trials of other antidementia agents and other CNS drugs (i.e. antidepressants).[27] There were no differences in pairwise comparisons between placebo versus the donepezil 5- and 10-mg/d group mean change

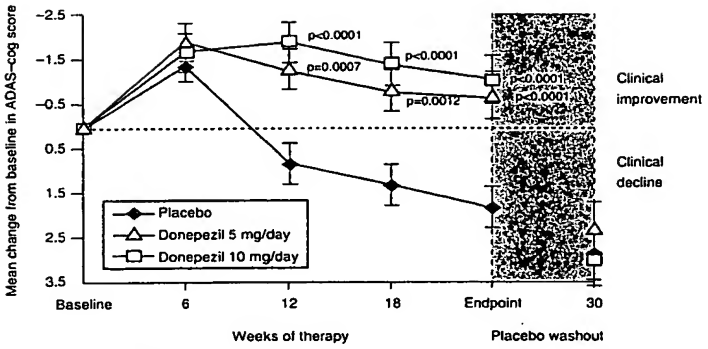

Figure 1. Mean (± SEM) change from baseline in ADAS-cog score for 5- and 10-mg/d-donepezil- and placebo-treated patients with mild to moderate Alzheimer's disease.

scores at the first 6-week visit. However, thereafter, the ADAS-cog performance for donepezil-treated patients did not deteriorate with time, thus generating a statistically significant treatment effect versus placebo at the 12-, 18-, and 24-week visits and at study endpoint (see figure 1).

Mean changes in ADAS-cog scores at study endpoint in the donepezil-treated groups revealed a dose-response relationship. An improvement of −0.67 and −1.06 in ADAS-cog scores from baseline was observed for the 5- and 10-mg/d-donepezil groups, respectively, whereas the placebo group deteriorated 1.82 points (table 2). Mean drug-placebo differences were −2.49 and −2.88 for the 5- and 10-mg/d dose groups, respectively ($p < 0.0001$) (see table 2, figure 1).

The percentages of patients in each group with poorer cognitive test performance on the ADAS-cog in the endpoint analysis relative to baseline were placebo, 42.3%; donepezil 5 mg/d, 20.3%; and donepezil 10 mg/d, 18.9%, suggesting that at least 80% of patients receiving donepezil did not experience cognitive worsening as compared with 57.7% of placebo patients over the 24 weeks of treatment (figure 2). Because no measurable decline in cognition (as assessed by ADAS-cog) is considered to be a clinical benefit in a progressive condition such as AD, treatment with donepezil provides obvious clinical benefit.

An improvement of four points or greater in ADAS-cog score versus baseline was seen in 26.8% of placebo, 37.8% of the 5-mg/d, and 53.5% of the 10-mg/d treated patients (see figure 2). Improvement of seven points or greater versus baseline at study endpoint was seen in 25.2% of the 10-mg/d-donepezil group, 15.4% of the 5-mg/d-donepezil group, and only in 7.8% of the placebo group.

Primary efficacy parameters: CIBIC plus. Beginning at the week 12 assessment and continuing throughout

***Table 2** Results (means at study endpoint) of pairwise comparisons for primary and secondary efficacy variables (ITT-LOCF analyses)*

	ADAS-cog			CIBIC plus		
	Placebo (n = 153)	Donepezil 5 mg/d (n = 152)	Donepezil 10 mg/d (n = 150)	Placebo (n = 152)	Donepezil 5 mg/d (n = 149)	Donepezil 10 mg/d (n = 149)
Primary efficacy variables						
Mean baseline score*†	27.28 ± 0.96	26.28 ± 0.96	27.41 ± 0.86	—	—	—
Endpoint: mean ADAS-cog change from baseline/CIBIC plus value at endpoint*	1.82 ± 0.49	−0.67 ± 0.51	−1.06 ± 0.51	4.51 ± 0.08	4.15 ± 0.09	4.07 ± 0.07
Drug-placebo difference		−2.49	−2.88		0.36	0.44
p (treatment vs. placebo)‡		<0.0001	<0.0001		0.0047	<0.0001
Mean change at 30 weeks*§	2.91 ± 0.57	2.29 ± 0.56	2.96 ± 0.64	4.73 ± 0.09	4.48 ± 0.10	4.78 ± 0.10
	MMSE			CDR-SB		
	Placebo (n = 154)	Donepezil 5 mg/d (n = 153)	Donepezil 10 mg/d (n = 150)	Placebo (n = 153)	Donepezil 5 mg/d (n = 154)	Donepezil 10 mg/d (n = 151)
Secondary efficacy variables						
Mean baseline score*†	19.40 ± 0.37	19.44 ± 0.38	19.17 ± 0.37	6.98 ± 0.19	7.11 ± 0.19	7.13 ± 0.19
Endpoint: mean change from baseline*	−0.97 ± 0.28	0.24 ± 0.29	0.39 ± 0.29	0.58 ± 0.14	−0.01 ± 0.14	−0.02 ± 0.14
Drug-placebo difference		1.21	1.36		0.59	0.60
p (treatment vs. placebo)		0.0007	0.0002		0.0008	0.0007
Mean change at 30 weeks*§	−1.18 ± 0.31	−0.40 ± 0.30	−0.97 ± 0.34	0.66 ± 0.16	0.21 ± 0.16	0.34 ± 0.18

* Values are means ± SEM.

† Mean baseline score at randomization.

‡ Despite the difference in age between the groups, the treatment by age interaction was not found to be significantly significant. An ANCOVA model where response = overall means + baseline score + age at baseline + treatment effect + site effect + random effect was used as the primary model to test for overall treatment effect using type III sums of squares.

§ Means are the change from baseline at 30 weeks after a 6-week, single-blind washout.

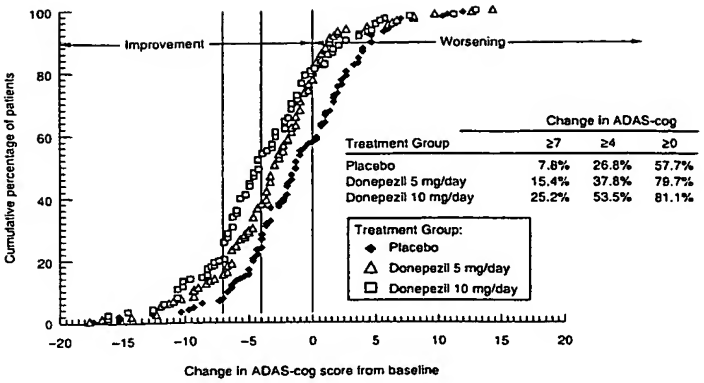

Figure 2. Cumulative percentage of patients with specified changes from baseline in ADAS-cog scores.

double-blind treatment, both the 5- and 10-mg/d-donepezil treatment groups exhibited improvement in global function relative to placebo ($p \leq 0.005$ at endpoint; figure 3). The differences in mean drug-placebo CIBIC plus scores at endpoint were dose dependent at 0.36 for the 5- and 0.44 for the 10-mg/d dosing groups. The strength of these results can be seen by examining the percentage of patients who were scored as improved on drug compared with placebo at study endpoint. Only 11% of placebo patients, as compared with 26% of the 5-mg/d and 25% of the 10-mg/d donepezil-treated patients were scored as improved (CIBIC plus ≤ 3). Overall, donepezil increased the number of treatment successes (CIBIC plus ≤ 4). Furthermore, donepezil reduced the number of treatment failures (CIBIC plus ≥ 5; $p = 0.0018$); the percentage of patients who had failed visits at least half the time were 45% in the placebo, 33% in the 5-, and 25% in the 10-mg/d-donepezil groups. After the 6-week-long, single-blind placebo washout, similar to the means of the ADAS-cog scores (see figure 1), the CIBIC plus ratings for both donepezil groups declined to levels that were not significantly different from the means of the placebo group (see figure 3), indicating that this beneficial effect of donepezil relies on its continued administration.

Secondary efficacy parameters. Donepezil treatment groups demonstrated a dose-dependent improvement in MMSE scores compared with placebo ($p \leq 0.0007$; figure 4) with mean drug-placebo differences of 1.21 for the 5- and 1.36 for the 10-mg/d-donepezil groups (see table 2).

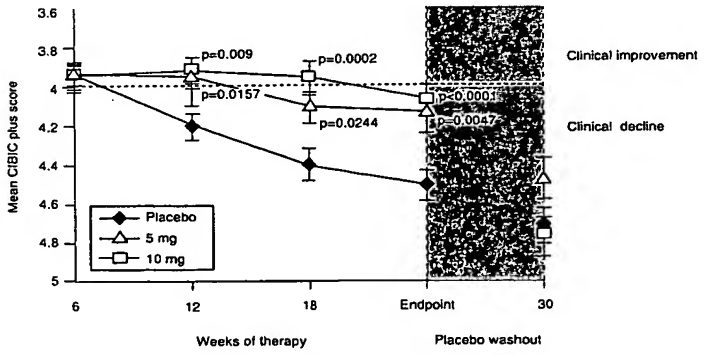

Figure 3. Mean (± SEM) CIBIC plus score for 5- and 10-mg/d-donepezil- and placebo-treated patients with mild to moderate Alzheimer's disease.

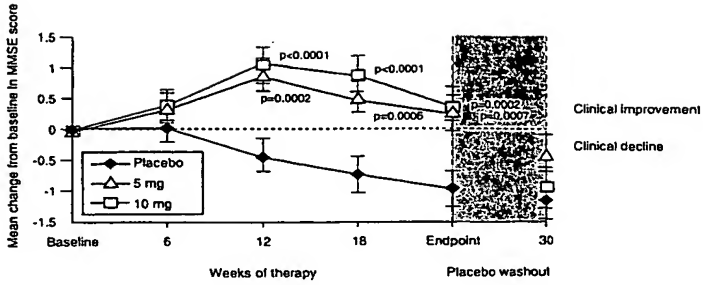

Figure 4. Mean (± SEM) change from baseline in MMSE score for 5- and 10-mg/d-donepezil- and placebo-treated patients with mild to moderate Alzheimer's disease.

Furthermore, improvements were observed in CDR-SB scores at weeks 18 and 24, plus at study endpoint ($p \leq 0.0008$; figure 5) with a mean drug-placebo difference for both the 5- and 10-mg/d-donepezil treatment groups of 0.6 (see table 2). Patient perceptions of their well-being as measured by the QoL scale showed a trend for improvement for both dose groups versus placebo by the 12-week visit and the improvement was sustained throughout the 18- and 24-week visits. However, only the 5-mg/d-dose group achieved significant improvement and this was only at week 24 ($p = 0.05$) (figure 6). Significant differences were not evident at study endpoint.

After the 6-week, single-blind placebo washout phase at the end of this study, scores on all measures declined to values that were not statistically different from placebo. There was no evidence of "overshoot" or decline in clinical state that was worse than that of patients who received placebo for the entire trial, suggesting that abrupt drug withdrawal did not cause exacerbation of symptoms or adverse effects. Interestingly, analyses of the CDR-SB data after placebo washout in this trial suggested residual benefits for both the 5- and 10-mg/d-donepezil groups when compared with the placebo group (see figure 5). However, this is not thought to signify any lingering pharmacodynamic activity of donepezil, especially because other efficacy parameters had returned to baseline values at the same time point, but rather the insensitivity of the assessment tool to quantify the degree of change.

Safety. The percentages of patients completing the study on their originally assigned treatment regimen were placebo, 80%; donepezil 5 mg/d, 85%; and donepezil 10 mg/d, 68%. The percentages of the patients in the groups

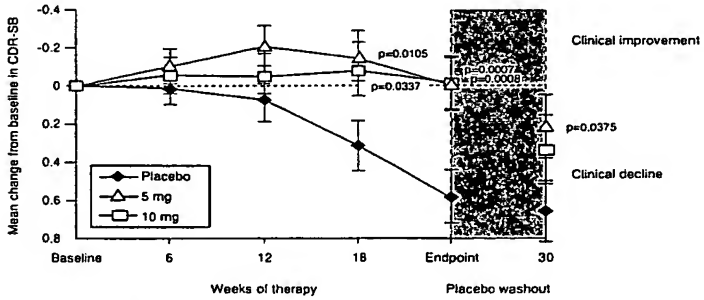

Figure 5. Mean (± SEM) change from baseline in CDR-SB score for 5- and 10-mg/d-donepezil- and placebo-treated patients with mild to moderate Alzheimer's disease.

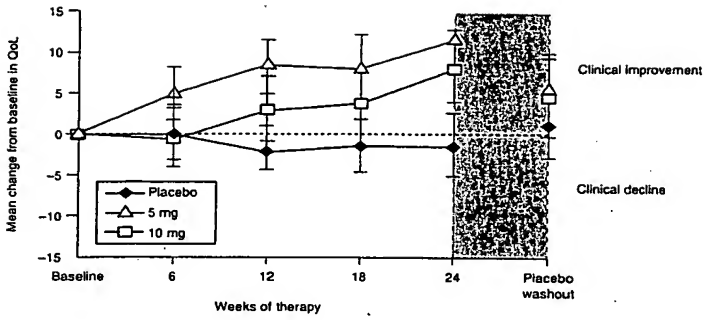

Figure 6. Mean (± SEM) change from baseline in QoL score for 5- and 10-mg/d-donepezil- and placebo-treated patients with mild to moderate Alzheimer's disease.

who discontinued the study because of an adverse event were placebo, 7%; donepezil 5 mg/d, 6%; and donepezil 10 mg/d, 16%. Only cholinergic-related effects, anticipated from the mode of action of this drug, were seen in significantly higher percentages of donepezil-treated patients as compared with the placebo group (table 3). Most of these adverse events were transient and of mild severity, except for nausea and vomiting that, although transient, were occasionally of moderate severity. The percentage of patients affected by cholinergic side effects was generally larger in the donepezil 10-mg/d group. The higher incidence of cholinergic side effects experienced in the 10-mg/d group was due to the forced, rapid titration schedule used in this study. In an open-label study of patients who received placebo in double-blind trials (n = 269), where the dose of donepezil was escalated to 10 mg/d after 4 to 6 weeks at 5 mg/d, the incidence of these cholinergic events was reduced to that experienced by the 5-mg/d-donepezil and placebo groups (Aricept, Eisai Inc., [donepezil hydrochloride tablets], package insert, Teaneck, NJ).

Table 3 Number (%) of patients with treatment-emergent signs or symptoms

Adverse event*	Placebo (n = 162)	Donepezil 5 mg/d (n = 154)	Donepezil 10 mg/d (n = 157)
Fatigue	3 (2)	8 (5)	12 (8)†
Diarrhea	11 (7)	14 (9)	27 (17)†
Nausea	6 (4)	6 (4)	26 (17)†
Vomiting	3 (2)	5 (3)	16 (10)†
Anorexia	3 (2)	3 (2)	11 (7)
Muscle cramps	1 (1)	9 (6)	12 (8)†
Dizziness	7 (4)	15 (10)	13 (8)
Rhinitis	4 (2)	1 (1)	9 (6)

* Treatment-emergent signs and symptoms were recorded by the COSTART body system and graded as mild, moderate, or severe (severity data not shown). All events are reported, whether or not considered related to treatment. Donepezil caused relatively little increase in adverse signs or symptoms as compared with placebo. Only cholinergic related effects were seen in significantly higher percentage of patients as compared with the placebo group. The percentage of patients affected was higher in the 10-mg/d group as compared with the 5-mg/d group, except for dizziness, which showed no relation to dose. Most of these events were mild or transient, except for nausea and vomiting, which were generally transient but of mild to moderate severity.

† $p \leq 0.05$. Overall p values were calculated only for preferred terms where the overall incidence rate was ≥5%.

Two patients died during this study: a placebo patient of pulmonary embolus and a patient in the 10-mg/d-donepezil treatment group, whose cause of death was determined to be poorly defined infection or possibly metastatic cancer of the liver. Neither of these deaths were considered to be related to treatment. Thirty-one patients (6%) experienced one or more serious adverse event during the study or within 1 month of its termination, with most considered not related to the study drug (table 4). Slightly more patients experienced serious adverse events in the 10-mg/d-donepezil group (15 patients; 10%) than in the 5-mg/d-donepezil (7 patient; 5%) or placebo (9 patients; 6%) groups. The percentages of adverse events judged as possibly related to treatment was lowest for the 10-mg/d group (24%). No events were judged probably or definitely related to treatment.

TEAVs were uncommon in this study. Analysis of liver function tests (alanine transaminase, aspartate transaminase, alkaline phosphatase, total bilirubin, and albumin) demonstrated that the incidence of clinically significant TEAVs for patients with 5 or 10 mg/d donepezil did not differ statistically from patients treated with placebo. The only statistically significant difference in any laboratory test parameter was due to reports of a low level of hemoglobin in four patients in the 10-mg/d-donepezil group ($p = 0.0232$) as compared with no patients in the 5-mg/d-donepezil or placebo groups. However, in two of these patients, the low values were due to pre-existing conditions. Thus, for treatment-emergent abnormalities, there were no differences among the treatment groups.

AChE inhibition. The mean percentage inhibition of RBC AChE at 6 weeks in the 5-mg/d-donepezil treatment group was 63.7% and for the 10-mg/d-donepezil treatment group was 77.3%. Neither of these means changed significantly in the subsequent 6-week measurements during the treatment phase, indicating the pharmacodynamics of donepezil were stable over the course of the study. The relationship between plasma donepezil concentrations and percentage AChE inhibition is shown in figure 7. A few data points show a 0% inhibition of RBC AChE inhibition even though a high plasma donepezil concentration was achieved. These occasional disparities were due to errors in sample processing and shipping from the study sites. E_{max} for rbc AChE inhibition was 98.43% and the EC_{50} was 13.4 ng/mL donepezil.

Discussion. This 24-week trial confirms that donepezil is efficacious in treating symptoms of memory and cognitive loss in patients with mild to moderately severe AD. Patients treated with donepezil demonstrated improvements in cognitive function, as measured by the ADAS-cog, and in global clinical function, as measured by the CIBIC plus, relative to placebo. Benefits in the donepezil-treated groups were also found using the MMSE, CDR-SB, and to a lesser extent QoL, confirming that there were cognitive and functional improvements associated with donepezil treatment that were maintained throughout the double-blind treatment period. There is evidence of a dose-response effect, with the done-

*Table 4 Serious adverse events**

Donepezil dose	Serious adverse event (COSTART preferred terms)	Relationship to drug
Placebo	Cholelithiasis, nausea, vomiting	Not related
	Basal cell carcinoma	Not related
	Cerebrovascular accident†	Not related
	Infarct myocardial	Not related
	Pain chest, dyspnea, diaphoresis	Not related
	Ischemia myocardial,‡ syncope	Possibly related§
	Joint disorder	Not related
	Embolus pulmonary†	Not related‖
	Abdominal disturbance,† gastrointestinal disorder†	Possibly related
	Bronchitis	Possibly related§
5 mg/day	Basal cell carcinoma	Not related
	Infection	Not related
	Angina pectoris	Possibly related§
	Premature ventricular contractions,† syncope,† dizziness†	Possibly related§
	Infection, pyelonephritis,† renal failure†	Possibly related§
	Joint disorder†	Not related
	Accident, pulmonary collapse	Not related
10 mg/day	Hernia†	Not related
	Pneumonia	Not related
	Accident, fracture bone	Not related
	Head pressure,† blood pressure oscillatory,† drooling,† ataxia,† dysarthria†	Possibly related
	Agitation†	Possibly related§
	Hernia	Not related
	Creatinine serum increased	Not related
	Carcinoma†	Not related
	Accident, fracture bone, hypoxia	Possibly related
	Accident,† fracture bone†	Not related
	Carcinoma breast	Not related
	Nausea, vomiting, dehydration, thrombosis venous deep	Possibly related
	Death†	Not related
	Accident,† fracture bone†	Not related
	Cerebrovascular accident†	Not related
	Syncope†	Not related

* Treatment relationship assigned under double-blind conditions.
† Patient withdrew because of this serious adverse event.
‡ Patient withdrew because of myocardial ischemia and two non-serious adverse events: movement disorder and psychosis.
§ Sponsor judged event "not related."
‖ Sponsor judged event "possibly related."

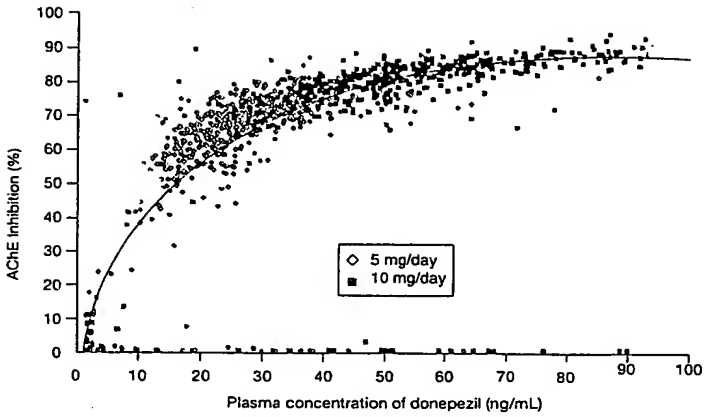

Figure 7. Correlation between plasma concentrations of donepezil and percentage RBC AChE inhibition (for all subjects at all visits where both determinants were evaluable).

pezil 10-mg/d patients showing somewhat greater improvement than the patients treated with donepezil 5 mg/d. Dose trend analyses using both Fisher's exact test and logistic regression indicate this dose-response is statistically significant ($p \leq 0.05$). The beneficial effects of donepezil became apparent at the 12-week visit and persisted with no decrease in magnitude at the 18- and 24-week visits and at study endpoint. The evaluable patient population and ITT analyses of these data gave very similar results, because a relatively small percentage of patients dropped out of this study for any reason.

Other ChE inhibitors have also shown efficacy in treating symptoms of AD but are often accompanied by significant or intolerable dose-related cholinergic side effects that have limited many patients' ability to continue treatment.[6,9,28,29] The high frequency of side effects may be partially attributed to peripheral inhibition of ChE by some agents. However, it may also be that the high rate of side effects is related to the high level of AChE inhibition necessary for positive cognitive effects and to rapid rates of fluctuation in AChE inhibition produced by these short-acting compounds. In comparison with the relatively short half-lives of some ChE inhibitors, the long half-life of donepezil (~70 hours) provides relative stability in the extent of AChE inhibition over the course of a day, which may also contribute to the relative reduction in cholinergic side effects seen with this drug. In addition to tolerance, the long half-life of donepezil allowed once-a-day dose administration in this trial. The convenience to caregivers probably contributed to the high levels of compliance and, in this study, to the high percentage of patients who completed the trial.

Previous studies of acridine-based ChE inhibitors have found evidence of hepatotoxicity in as many as 50% of patients, with levels three times greater than the upper limit of normal for alanine transaminase in 25% of patients.[6,9] As a consequence of the combined liability of cholinergic and hepatic side effects,

in a pivotal multicenter trial of tacrine versus placebo,[6] only 27% of patients in the highest dosage group (160 mg/d) were still available for an evaluable patient analysis at the end of the trial (30 weeks).

A relatively large treatment effect at 30 weeks was reported for the evaluable patient population in this tacrine trial, with the 160-mg/d-tacrine treatment group experiencing a 4.1-point improvement in ADAS-cog scores compared with placebo. For the ITT analysis, however, this improvement was reduced to approximately two points.[6] The 3.2-point mean at 24 weeks and the 2.9-point mean improvement seen by study endpoint in the ITT analysis of the high-dose donepezil (10 mg/d) group thus compares very favorably. To give perspective to the magnitude of these changes in ADAS-cog scores, the placebo cohort from this study had a 1.8-point deterioration, which is equivalent to an annualized rate of decline of approximately 3.9 points. This is lower than the average decline per year in untreated patients, because moderately severe untreated AD patients have been reported to decline by between 7 and 11 ADAS-cog points per year.[23,24] However, the instrument is not uniformly sensitive to change over the course of the disease with scores in mildly or severely demented patients increasing by only zero to five points per annum. Thus, performance of the placebo cohort in this study is consistent with these previous findings. For this reason, effect size in a controlled trial is more accurately determined as a percent of the annualized rate of decline of the placebo cohort of the trial. The treatment effect size for the two donepezil dose groups (drug-placebo difference expressed as a percent of placebo decline) represents about an 80% reduction of the annualized amount of cognitive decline in the placebo group.

A panel of experts convened by the FDA had previously suggested that an improvement of four points or more in ADAS-cog score with antidementia therapy would be considered a clinically significant effect.[30] Given that this criteria is influenced by the duration of the trial (given a long enough trial, no patient would have this benefit) and that it fails to consider the rate of decline in the corresponding placebo cohort (and, thus, the amount of movement expected on the ADAS-cog), it is not a meaningful way to judge the benefits of treatment. Approximately 40% of patients (160-mg/d group) completing the 30-week tacrine trial had ADAS-cog improvements of four points or greater. However, given the 73% dropout rate, only 12% of patients originally randomized to the 160-mg/d group achieved this standard of improvement. The change in placebo (in our trial) over 24 weeks is less than that seen in other studies. This may indicate that more mild patients were included here. However, 68% of the donepezil 10-mg/d patients completed this study and 53% of those completing had four points or greater improvement in ADAS-cog from baseline. Therefore, compared with the 12% from the tacrine study, three times as many patients, or 36%, achieved this level of benefit from donepezil.

It has been reported that ChE inhibitors (e.g., physostigmine and metrifonate) exhibit an inverted U-shaped curve when efficacy is plotted against percent inhibition of ChE and that clinical efficacy is obtained within a therapeutic window corresponding to 30 to 60% inhibition.[31-33] Hence, maximal clinical benefit would be gained at ~43% inhibition of AChE with actual worsening occurring at higher percentages of inhibition.[31-33] In the present study, the mean percentage inhibition of AChE, as measured by an RBC radioenzyme assay, was 63.7% for the 5-mg/d-donepezil group and 77.3% for the 10-mg/d group. The EC_{50} was seen at a plasma donepezil concentration of 13.4 ng/mL and a plateau of enzyme inhibition (80 to 90%) was attained at a higher plasma concentration. Thus, donepezil provides improved clinical efficacy even at relatively high levels of AChE inhibition.

The 10-mg/d-donepezil group, compared with placebo, showed the greatest change in mean ADAS-cog score versus placebo. Thus, it is possible that an even higher dosage of donepezil might further improve cognitive symptoms. However, doses of 10 mg/d produced rates of inhibition of AChE on the upper asymptote of the enzyme inhibition curve, suggesting that further increases in dose would provide only marginal increases in activity.

Twelve percent fewer of the 10-mg/d-donepezil treatment group completed the trial as compared with placebo, and the incidence of patients who discontinued the study because of adverse events was only 6% for the 5-mg/d group versus 16% for the 10-mg/d group. However, a rapid, forced titration schedule was used to increase the dosage in the 10-mg/d-donepezil group. Subsequent analysis from an open-label study of donepezil in donepezil-naïve patients has demonstrated that when a longer dosage titration schedule is used (escalation to 10 mg/d donepezil after 4 to 6 weeks at 5 mg/d), the occurrence of side effects is minimized. Indeed, by allowing achievement of steady-state concentrations at 5 mg/d before the elevation to 10 mg/d, the incidence of common adverse events was reduced, being comparable with that experienced by both the 5-mg/d-donepezil and placebo groups (Aricept [donepezil hydrochloride tablets], package insert). This is consistent with the side-effect profiles of many CNS agents, such as neuroleptics and tricyclic antidepressants, and is supported by similar findings from the tacrine trials. However, unlike the neuroleptics and tricyclics, no reverse titration is needed for donepezil. Abrupt discontinuation causes no adverse events and results in a gradual reduction of treatment benefit over 6 weeks.

The results of this trial demonstrate that donepezil improves both cognition and global function in patients with mild to moderately severe AD. It is well tolerated, with few patients having significant side effects. Donepezil would seem to have substan-

tial utility in treating patients with mild to moderate stage disease. The improvement in the CDR-SB scores in the donepezil-treated patients in this trial raises the possibility that donepezil may also positively affect functional activities of daily living. Future trials are necessary to determine if donepezil has significant effects in delaying deterioration or actually improving functional outcomes for AD patients. A drug that preserves function in patients' activities of daily living may help postpone the need for family and professional caring services, ultimately delaying nursing home placement and holding down the cost of caring for this increasing population.

Appendix

The Donepezil Study Group participants are as follows: Bruce Albala, Clinical Technologies Associates, Elmsford, NY; Barry Baumel, NeuroMedical Research Associates, Fort Lauderdale, FL; Gary Booker, LSU Medical Center, Shreveport, LA; James Dexter, University of Missouri, Columbia, MO; Mildred Farmer, Clinical Studies, St. Petersburg, FL; John P Feighner, Feighner Research Institute, San Diego, CA; Steven Ferris, NYU Medical Center, NY; Barry Gordon, Johns Hopkins University School of Medicine, Baltimore, MD; David G Gorman, Lovelace Science Resources, Inc., Albuquerque, NM; George Hanna, University of Virginia, Charlottesville, VA; Lindy E Harrell, The University of Alabama at Birmingham, Birmingham, AL; Richard Hubbard, Southwest Institute of Clinical Research, Rancho Mirage, CA; John Kennedy, Vanderbilt University Medical Center, Nashville, TN; F.C. Kinney, The University of Alabama at Birmingham, Birmingham, AL; James McCarthy, Clinical Studies, South Yarmouth, MA; Douglas W Scharre, Ohio State University, Columbus, OH; Frederick Schaerf, Clinical Studies, Fort Myers, FL; Lon Schneider, Hospital Place, Los Angeles, CA; Benjamin Seltzer, Tulane Medical School, New Orleans, LA; Alan Siegal, Center for Geriatric & Adult Psychiatry, Hamden, CT; Stuart R Stark, The Neurology Center, Alexandria, VA; Abbey Strauss, Clinical Studies, Boynton Beach, FL; Thomas M Walshe, Institute for Psychopharmacologic Research, Danvers, MA.

References

1. Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet 1976;2:1403.
2. Perry EK, Perry RH, Blessed G, Tomlinson BE. Necropsy evidence of central cholinergic deficits in senile dementia [letter]. Lancet 1977;1:189.
3. Whitehouse PJ, Price DL, Clark AW, Coyle JT, DeLong MR. Alzheimer's disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. Ann Neurol 1981;10:122–126.
4. Giacobini E, Becker R. Present progress and future development in the therapy for Alzheimer's disease. In: Iqbal K, Wisniewski HM, Winblad B, eds. Alzheimer's disease and related disorders. New York: Alan R Liss Inc., 1989:1121–1154.
5. Schneider LS, Farlow MR. Predicting response to cholinesterase inhibitors in Alzheimer's disease: possible approaches. CNS Drugs 1995;4:114–124.
6. Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI. For the Tacrine Study Group. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. JAMA 1994;271:985–991.
7. Farlow M, Gracon SI, Hershey LA, Lewis, KW, Sadowsky CH, Dolan-Ureno J. A controlled trial of tacrine in Alzheimer's disease. JAMA 1992;268:2523–2529.
8. Hardiman S, Miller K, Murphy M. Clinical trials with velnacrine: (PROPP) The physician reference of predicted probabilities—a statistical model for the estimation of hepatotoxicity risk with velnacrine maleate. Acta Neurol Scand 1993; 149(suppl):46–52.
9. Antuono PG, for the Mentane Study Group. Effectiveness and safety of velnacrine for the treatment of Alzheimer's disease: a double-blind, placebo-controlled study. Arch Intern Med 1995; 155:1766–1772.
10. Rogers SL, Yaminishi Y, Yamatsu K. E2020—the pharmacology of a piperidine cholinesterase inhibitor. In: Becker R, Giacobini E, eds. Cholinergic basis for Alzheimer therapy. Boston: Birkhäuser, 1991;314–320.
11. Rogers SL, Friedhoff LT, the Donepezil Study Group. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicenter, randomized, double-blind, placebo-controlled trial. Dementia 1996;7:293–303.
12. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services task force in Alzheimer's disease. Neurology 1984;34:939–944.
13. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Revised. Washington, DC: American Psychiatric Association, 1987.
14. Folstein NF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
15. Hughes CD, Berg L, Danziger L, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566–572.
16. Rosen WG, Mohs RC, Davis K. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–1364.
17. Schneider LS, Olin JT, Doody RS, et al. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. AD Assoc Dis 1997;11(suppl 2):S22–32.
18. Blau TH. Quality of life, social indicators and criteria of change. Prof Psychol 1977;8:464–473.
19. Berg L, Miller JP, Baty J, Rubin EH, Morris JC, Figiel G. Mild senile dementia of the Alzheimer type. 4. Evaluation of intervention. Ann Neurol 1992;31:242–249.
20. Lee JW, Rogers SL, Friedhoff LT, Cooper NM. Validation and application of an HPLC method for the determination of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine HCl (E2020) in human plasma. Pharmaceutical Res 1992;9: S350.
21. Hulse JD, Rogers SL, Friedhoff LT, Sukovaty R, Pedersen JE, Lee JW. A radioenzyme assay of acetylcholinesterase activity in red blood cells and its correlation with 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine HCI. Pharmaceutical Res 1992;9:S228.
22. Mohs RC, Davis BM, Johns CA, et al. Oral physostigmine treatment of patients with Alzheimer's disease. Am J Psychiatry 1985;142:28–33.
23. Stern, RG, Mohs RC, Davidson M, et al. A longitudinal study of Alzheimer's disease: measurement, rate and predictors of cognitive deterioration. Am J Psychiatry 1994;151:390–396.
24. Kramer-Ginsberg E, Mohs RC, Aryan M, et al. Clinical predictors of course of Alzheimer's patients in a longitudinal study: a preliminary report. Psychopharmacol Bull 1988;24:458–462.
25. Leber P. US Food and Drug Administration, Center for Drug Evaluation and Research, Division of Neuropharmacological Drug Products. Form and contents of NDA reviews: strategies for the efficacy analysis. November 5, 1985.
26. US Food and Drug Administration, Center for Drug Evaluation and Research, Office of Epidemiology and Biostatistics. COSTART: coding symbols for thesaurus of adverse reaction terms. 4th edition, 1993; Pub. PB93-209138.
27. Knopman D, Gracon S. Observations on the short-term "natural history" of probable Alzheimer's disease in a controlled clinical trial. Neurology 1994;44:260–265.
28. Thal LJ, Schwartz G, Sano M, et al. A multicenter double-blind study of controlled-release physostigmine for the treat-

ment of symptoms secondary to Alzheimer's disease. Neurology 1996;47:1389–1395.
29. Canal N, Franceschi M, Italian Eptastigmine Investigators. Eptastigmine (MF-201). A double-blind, placebo-controlled clinical trial in Alzheimer's disease patients. In: Giacobini E, Becker R, eds. Alzheimer's disease: therapeutic strategies. Boston: Birkäuser, 1994;108–112.
30. Peripheral and Central Nervous System Drugs Advisory Committee Meeting, July 7, 1989. Rockville MD: Dept of Health and Human Services, Public Health service, Food and Drug Administration; 1989:227.
31. Thal LJ, Maasur DM, Fuld PA, Sharpless NS, Davies P. Memory improvement with oral physostigmine and lecithin in Alzheimer's disease. In: Katzman R, ed. Banbury report: biological aspects of Alzheimer's disease. 9th ed. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 1983:461–470.
32. Becker R, Colliver J, Elble R, et al. Effects of metrifonate, a long acting cholinesterase inhibitor in Alzheimer's disease: report of an open trial. Drug Dev Res 1990;19:425–434.
33. Becker R. The second generation of cholinesterase inhibitors: clinical and pharmacological effects. In: Becker R, Giacobini E, eds. Cholinergic basis for Alzheimer therapy. Boston: Birkhäuser, 1991;263–296.

Sulcal variability in the Alzheimer's brain

Correlations with cognition

M.S. Mega, MD, PhD; P.M. Thompson, MS; J.L. Cummings, MD; C.L. Back, PhD; M.L. Xu; S. Zohoori; A. Goldkorn, BS; J. Moussai, BS; L. Fairbanks, PhD; G.W. Small, MD; and A.W. Toga, PhD

Article abstract—We mapped the three dimensional (3D) extents and variability of selected sulci in the Alzheimer's brain and explored the relationship between sulcal pattern and patient's cognitive performance. High-resolution MRIs of 10 patients with probable Alzheimer's disease (AD) were linearly transformed into a standard "normalized" 3D atlas (known as the Talairach coordinate system) and, on each relevant slice, contours of the left and right Sylvian fissure, anterior and posterior calcarine, callosal, parietooccipital, and cingulate sulci and the floor of the temporal horn of the lateral ventricle were traced. These landmarks were chosen because of their relative invariant location across individuals and because they demarcate functional boundaries relevant in AD. The sulcal contours were resolved into two-dimensional surfaces that cut through a brain volume. All 10 patients' sulcal surfaces were averaged to determine their mean spatial locations in the Talairach coordinate system. The 3D spatial extents of each patient's sulci were compared with their disease severity based on neuropsychological performance. The 3D sulcal variability, within the "normalized" atlas space, ranged from 4.0 mm for the left callosal sulcus to 9.1 mm for the left Sylvian fissure. Significant correlations were found among the spatial extents for the posterior floor of the right temporal horn of the lateral ventricle ($r = -0.89$, $p < 0.001$ for vertical extent) and right anterior calcarine sulcus ($r = -0.75$, $p < 0.01$ for anterior-posterior extent) with copying ability of the Rey-Osterrieth Complex Figure; the right anterior calcarine also had a significant relationship ($r = -0.72$, $p = 0.02$ for anterior-posterior extent) with performance on the Block Design subtest from the Wechsler Adult Intelligence Scale–Revised. Verbal fluency performance measured by the Controlled Oral Word Association Test was significantly related to the left cingulate ($r = 0.91$, $p < 0.001$ for anterior-posterior extent, and $r = -0.82$, $p < 0.01$ for vertical extent) and right cingulate ($r = -0.72$, $p \leq 0.02$ for vertical extent) sulci. This exploratory study is the first to evaluate the relationship between 3D sulcal variability and cognition; our preliminary findings suggest that the 3D pattern of sulci in the AD brain is related to the severity of the disease as reflected by cognitive performance. In the Talairach brain atlas, sulcal variability, within an AD population, approaches 1 cm. This large variability requires correction when functional imaging data are transformed into the Talairach atlas space to "normalize" individual morphologic differences.

NEUROLOGY 1998;50:145–151

The pathologic process in Alzheimer's disease (AD)—reflected by the concentration of neurofibrillary tangles (NFTs) and senile plaques—has a distinct regional predilection. The entorhinal cortex and subiculum/CA1 zone of the hippocampal formation are the first to manifest NFTs[1,2]; as the disease progresses, heteromodal association cortices are affected. The pathologic stages of AD follow the transi-

From the Department of Neurology, Laboratory of Neuro Imaging (Drs. Mega, Thompson, and Toga and M.L. Xu, S. Zohoori, A. Goldkorn, and J. Moussai), Alzheimer's Disease Center (Drs. Mega, Cummings, Back, Fairbanks, Small, and Toga), Department of Psychiatry and Biobehavioral Sciences (Drs. Cummings, Back, Fairbanks, and Small), and Center on Aging (Dr. Small), UCLA School of Medicine, Los Angeles, CA.

Supported by an NIA Grant (K08AG100784) (to M.S.M.); the Howard Hughes Institute, Fulbright Commission, and Grant No. G-1-00001 of the United States Information Agency (to P.M.T.); Human Brain Project (NIMH/NIDA: P20MH/DA 52176, NSF (BIR9322434), NLM (LM/MH05639), and NCRR (RR05956) (to A.W.T.); an Alzheimer's Disease Center grant (AG 10123) (to J.L.C. and M.S.M.); and an NIMH (1R01 MH52453), NIA (1R01 AG13308), and Alzheimer's Association (IIRG-94-101) grant (to G.W.S.).

Received May 15, 1997. Accepted in final form July 30, 1997.

Address correspondence and reprint requests to Dr. Arthur W. Toga, Laboratory of NeuroImaging, Department of Neurology, UCLA School of Medicine, 710 Westwood Plaza, Rm 4-238 Reed, Los Angeles, CA 90024-1769.

ORIGINAL INVESTIGATION

Donepezil Improves Cognition and Global Function in Alzheimer Disease

A 15-Week, Double-blind, Placebo-Controlled Study

Sharon L. Rogers, PhD; Rachelle S. Doody, MD, PhD; Richard C. Mohs, PhD; Lawrence T. Friedhoff, MD, PhD; and the Donepezil Study Group

Background: Donepezil hydrochloride (Aricept) is a selective acetylcholinesterase inhibitor developed for the treatment of Alzheimer disease. This phase 3 study was 1 of 2 pivotal trials undertaken to establish the efficacy and safety of using donepezil in patients with mild to moderately severe Alzheimer disease.

Objectives: To further examine the efficacy and safety of using donepezil in the treatment of patients with mild to moderately severe Alzheimer disease. To examine the relationships between plasma donepezil concentrations, inhibition of red blood cell acetylcholinesterase activity, and clinical response.

Methods: This was a 12-week, double-blind, placebo-controlled, parallel-group trial with a 3-week single-blind washout. Outpatients at 23 centers in the United States were randomized to receive placebo, 5 mg of donepezil hydrochloride, or 10 mg of donepezil hydrochloride (5 mg/d during week 1 then 10 mg/d thereafter) administered once daily at bedtime. Primary efficacy was measured using the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) and Clinician's Interview–Based Impression of Change including caregiver information (CIBIC plus).

Results: A total of 468 patients entered the study, more than 97% of whom were included in the intention-to-treat (end point) analyses. The use of donepezil produced statistically significant improvements in ADAS-cog, CIBIC plus, and Mini-Mental State Examination scores, relative to placebo. The mean drug-placebo differences, at end point, for the groups receiving 5 mg/d and 10 mg/d of donepezil hydrochloride were, respectively, 2.5 and 3.1 units for ADAS-cog ($P<.001$); 0.3 and 0.4 units for CIBIC plus ($P\leq.008$); and 1.0 and 1.3 units for Mini-Mental State Examination ($P\leq.004$). On the CIBIC plus scale, 32% and 38% of patients, respectively, treated with 5 mg/d and 10 mg/d of donepezil hydrochloride demonstrated clinical improvement (a score of 1, 2, or 3) compared with placebo (18%). The mean (± SEM) donepezil plasma concentrations at study end point were 25.9 ± 0.7 ng/mL and 50.6 ± 1.9 ng/mL in the groups receiving dosages of 5 mg/d and 10 mg/d, respectively. Corresponding mean (± SEM) percentages of inhibition of red blood cell acetylcholinesterase activity were 63.9% ± 0.9% and 74.7% ± 1.2% for these 2 dosages, respectively. There was a statistically significant positive correlation between plasma concentrations of donepezil and acetylcholinesterase inhibition; the EC_{50} (50% effect) was obtained at a concentration of 15.6 ng/mL. A plateau of inhibition (80%-90%) was reached at plasma donepezil concentrations higher than 50 ng/mL. The correlations between plasma drug concentrations and both ADAS-cog ($P<.001$) and CIBIC plus ($P = .006$) were also statistically significant, as were the correlations between red blood cell acetylcholinesterase inhibition and change in ADAS-cog ($P<.001$) and CIBIC plus ($P = .005$). The incidence of treatment-emergent adverse events with both dosages of donepezil (68%–78%) was comparable with that observed with placebo (69%). The use of 10 mg/d of donepezil hydrochloride was associated with transient mild nausea, insomnia, and diarrhea. There were no treatment-emergent clinically significant changes in vital signs or clinical laboratory test results. More important, the use of donepezil was not associated with the hepatotoxic effects observed with acridine-based cholinesterase inhibitors.

Conclusion: Donepezil hydrochloride (5 and 10 mg) administered once daily is a well-tolerated and efficacious agent for treating the symptoms of mild to moderately severe Alzheimer disease.

Arch Intern Med. 1998;158:1021-1031

The affiliations of the authors appear in the Acknowledgment section at the end of the article. Members of the Donepezil Study Group are listed on page 1024.

ALZHEIMER disease (AD) is a progressive dementing disorder that primarily affects the elderly population. Approximately 5% to 10% of the population older than 65 years and as many as 50% of those older than 85 years are estimated to have the disease.[1] Although little is known regarding the cause of AD, it is generally accepted that many of its symptoms are related to a cholinergic deficit in the cerebral cortex and other areas of the brain.[2-4] Indeed, the extent of neuropathological features, eg, cortical atrophy and the presence of amyloid plaques and neurofibrillary

PATIENTS AND METHODS

PATIENT POPULATION

Male and female patients of any race who were 50 years of age or older were recruited into the study by 23 centers in the United States. A diagnosis of probable AD was required to be consistent with the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria[16] and the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* categories 290.00 or 290.10.[17] The patients had mild to moderately severe disease as defined by Mini-Mental State Examination (MMSE)[18] scores of 10 to 26, and screening and baseline Clinical Dementia Rating (CDR) scores of 1 or 2.[19] All patients underwent computed tomography or magnetic resonance imaging within 6 months of entry. None of the patients had AD that was complicated by an additional diagnosis of delusions, delirium, or depression, and none had a known or suspected history of alcoholism or drug abuse. The patients were required to be ambulatory, or ambulatory when aided by either a walker or cane, and to have sufficient vision and hearing to enable them to comply with the study procedures.

Patients with any of the following major medical illnesses were specifically excluded from entering the trial: type 1 diabetes, obstructive pulmonary disease, or asthma; hematologic or oncologic disorders in the previous 2 years; or vitamin B_{12} or folate deficiency. Patients were also excluded if they had clinically significant active gastrointestinal, renal, hepatic, endocrine, or cardiovascular system disease that was not well controlled by diet, pharmacological treatment, or other therapeutic intervention. Patients with evidence of other psychiatric or neurologic disorders (eg, stroke, schizophrenia, or Parkinson disease), and those with a Hachinski ischemia score of 5 or more or known hypersensitivity to cholinesterase inhibitors were also excluded.

The study was conducted in accordance with Good Clinical Practice guidelines and the principles stated in the Declaration of Helsinki. Informed consent was obtained from the patients and also from the caregivers prior to any detailed screening procedures. The study adhered to the institutional review board policies at each site.

STUDY DESIGN

Our study had a randomized, double-blind, placebo-controlled, parallel-group design. Eligibility for inclusion in the trial was assessed during the screening phase that preceded the treatment period by a maximum of 2 weeks.

Patients were randomized to receive 12 weeks of treatment with placebo or 5 mg or 10 mg of donepezil hydrochloride administered once daily at bedtime. Each dose of study medication consisted of 2 tablets: 2 placebo tablets (placebo group); one 5-mg tablet and 1 placebo tablet (5-mg/d donepezil hydrochloride group); or two 5-mg tablets (10-mg/d donepezil hydrochloride group). To minimize the likelihood of reactions to acute extensive inhibition of AChE, a dosage of 10 mg was initiated using a blinded, forced titration scheme in which subjects received a dosage of 5 mg/d of donepezil hydrochloride for the first 7 days and a dosage of 10 mg/d for the remainder of the study. At the end of the double-blind treatment, all patients began a 3-week, single-blind washout period with placebo.

Use of any concomitant medications that could affect functioning of the central nervous system or interfere with efficacy assessments was prohibited. This included the use of any anticholinergic, cholinomimetic, anticonvulsant, antidepressant, antipsychotic, antianxiety, or stimulating agents, as well as anti-Parkinson and certain antihypertensive agents. Occasional use of other medications, such as hypnotics and cold preparations (prescription and over-the-counter sympathomimetic amines and antihistamines) was allowed, but not within 48 to 72 hours of a clinic visit. None of the patients had received investigational medications within 1 month of study entry. Approximately 90% of patients received allowable concomitant medication during the study.

Efficacy and safety assessments were undertaken at 3-week intervals throughout the trial. Treatment compliance was checked at each visit by counting the number of returned tablets and dividing by the number of treatment days. As specified by the protocol, patients were considered compliant when 80% or more of the required medication had been taken. Compliance was used as one of the determinants of the evaluable patient population.

OUTCOME MEASURES

The primary efficacy parameters used were the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog),[20] and a Clinician's Interview-Based Impression of Change scale that included caregiver-supplied information (CIBIC plus).[21]

The ADAS-cog is a sensitive and reliable psychometric scale. It consists of 11 items that evaluate selected aspects of memory, orientation, attention, language, reasoning, and praxis. Scores range from 0 (no impairment) to 70 (very severe impairment). To reduce the potential for practice or carryover effects at subsequent visits, different word lists were used.

The CIBIC is not a specific test instrument, but a technique that uses information obtained during an independent clinical interview to assess disease severity and progression of illness. A variety of CIBIC formats exist, each varying in terms of depth and structure. The format chosen for the donepezil clinical trials was a slightly modified version of the Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change.[21] This rating scale assesses patient function in 4 areas—general, cognitive, behavioral, and activities of daily living—through examination of 15 separate domains. Interviews with both the patient and caregiver are conducted by a clinician who is blinded from knowledge of other aspects of the study, including the results of other test procedures, clinical laboratory values, and adverse event reports. Disease severity is rated at baseline (CIBIS plus). Using the baseline interview as the sole source for comparison, patients are reexamined at subsequent visits to determine whether their conditions have changed. The change from baseline at subsequent visits (CIBIC plus) is scored by the same interviewer using a 7-point Likert-type scale, in which 1 represents markedly improved; 4, no change; and 7, markedly worse.

The secondary efficacy variables were the MMSE,[18] the Sum of the Boxes of the Clinical Dementia Rating

(CDR-SB)[22] and a quality of life (QoL) assessment.[23] The MMSE is a brief psychometric test conducted by a trained clinician or psychometrician who evaluates the cognitive state of the patient, including aspects of memory, orientation, language, and praxis. The CDR-SB is a global scale that assesses 6 domains of patient function (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). The CDR-SB was conducted as a consensus assessment by each patient's treatment team, except the CIBIC plus interviewer, and was based on information obtained from all procedures conducted during a clinic visit. The QoL assessment was a 7-item patient-rated scale that evaluated the patients' perceptions of their well-being in terms of relationships, eating and sleeping, and social and leisure activities. The test was conducted through patient interviews by a nurse evaluator or another clinician. The items were scored by marking on an analog scale between 2 anchor points: the extremes were 0 (worst quality) and 50 (best quality). Although this instrument has not been validated in patients with AD, it was selected because no QoL instrument has been validated in this patient population.

THERAPEUTIC DRUG MONITORING

Plasma concentrations of donepezil were measured from blood samples collected at each clinic visit using a sensitive and specific high-performance liquid chromatographic procedure, with UV detection.[24] The AChE activity in RBC membranes was measured from the same blood samples using a radioenzyme method.[25] Standard curves of the percentage of AChE inhibition vs the natural logarithm of the donepezil concentration (nanograms per gram of RBCs) were constructed using a third-order polynomial equation.

SAFETY ASSESSMENTS

Adverse events were elicited at each visit by questioning both the patient and the caregiver generally about the patient's status, and through direct observation by the patient treatment team. All adverse events reported or observed were recorded, along with the date and time of onset and cessation, plus assessments of severity and the likelihood of their being related to treatment.

Supine and standing blood pressures and heart rate were measured at screening and at the end of the washout phase. Sitting measurements were recorded at other visits. Hence, no quantitative data on the potential effects of donepezil on orthostatic hypotension were obtained. A standard 12-lead electrocardiogram was obtained at the start and end of the double-blind treatment.

Clinical laboratory evaluations were conducted at each clinic visit. Hematologic assessments included hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, RBC count, white blood cell count, differential cell count, and platelet count. Clinical chemistry tests included assessment of liver function (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin), renal function (creatinine and serum urea nitrogen), metabolic status (glucose, total protein, albumin, and cholesterol), electrolytes (sodium, potassium, chloride, phosphorus, and calcium), and cardiac enzymes (creatine kinase and lactate dehydrogenase). Routine dipstick urinalysis was performed (pH, glucose, protein, hemoglobin or blood, and ketones), along with specific gravity and microscopic examination of the sediment.

STATISTICAL ASSESSMENTS

The planned study population of 150 patients per group was based on a review of clinical studies of other cholinesterase inhibitors and the results of a previous phase 2 study with donepezil.[11] The sample size was intended to provide 80% power to detect a 0.27-point difference in the mean CIBIC plus scores for donepezil treatment groups compared with the placebo group at the 5% level of significance and assuming a patient completion rate of 80%. It was assumed that the dosages of 5 mg/d and 10 mg/d of donepezil hydrochloride would have equal efficacy. Therefore, this study was not powered to detect a difference between the active treatments but only between placebo and each active treatment group. This assumption was based on the results of a prior study[11] that evaluated dosages up to 5 mg/d and a review of studies of other cholinesterase inhibitors.

The primary analyses of efficacy and safety were performed on the intention-to-treat (ITT) population. For the safety analysis, this included all patients who were randomized to receive treatment, while the analysis of efficacy (that requires calculation of change from baseline scores) included all patients who had at least 1 postbaseline evaluation while undergoing treatment. The primary analysis was conducted on the end point data set. End point was week 12 for patients completing the double-blind portion of the study. For those who did not complete the study, their last observation while undergoing treatment was carried forward (LOCF) and used as the end point value. Secondary analyses were also undertaken in the fully evaluable population to confirm the conclusions of the primary ITT analysis. Fully evaluable patients were those who completed the 12-week period of double-blind treatment and who had at least 80% medication compliance at the week 12 visit and at a minimum of 2 other visits during the trial.

For continuous efficacy variables (ADAS-cog, MMSE, CDR-SB, and QoL), a general linear model was used to construct analysis of covariance models to compare the treatment groups with respect to changes from baseline in efficacy variables.[26] After confirming the assumptions underlying analysis of covariance, the reduced model contained effect for baseline score (covariate), treatment effect, and center effect. Type III sums of squares were used to determine statistical significance among the 3 treatment groups. In cases where differences existed, pairwise comparisons of the groups were undertaken using Fisher 2-tailed least significant difference procedure. The categorical efficacy variable, the CIBIC plus, was analyzed using the Cochran-Mantel-Haenszel test, with RIDITS as the score option.[27,28] The Cochran-Mantel-Haenszel test included adjustment for center.

Nonlinear regression analyses using a maximum-effect (E_{max}) model (AChE inhibition % = $EC_{max} \times$ donepezil/[EC_{50} + donepezil]) were undertaken to correlate plasma donepezil concentrations with inhibition of AChE activity (EC_{50} is the concentration where 50% effect is observed). Similar analyses were performed to investigate the

Continued on next page

association between AChE activity and primary efficacy outcomes (ie, ADAS-cog and CIBIC plus).

Intragroup changes in vital signs (baseline vs end point) were analyzed using paired *t* tests, and between-treatment differences were detected by analysis of variance. The analysis of adverse events was confined to treatment-emergent signs and symptoms (TESS) that began during or after administration of the first dose of study medication, or became more severe during treatment. Events, recorded using investigator terminology, were grouped and coded into common terms using a modified COSTART dictionary.[29]

The incidences of TESS and treatment-emergent laboratory test abnormalities (ie, newly occurring or clinically significant exacerbations of preexisting abnormalities) were compared among treatment groups using the Fisher exact test.

Statistical analyses were undertaken using SAS statistical software version 6 or higher (SAS Institute Inc, Cary, NC). All hypothesis tests were 2-sided, and *P* values of .05 or less were considered to be statistically significant.

tangles, and the severity of memory and cognitive impairments have been found to correlate with cholinergic loss in the central nervous system.[3] These findings suggest that augmentation of cholinergic function might improve clinical symptoms. To this end, various pharmacological agents have been developed.

For editorial comment see page 941

To date, perhaps the most widely investigated agents for the treatment of AD are cholinesterase inhibitors, which act by inhibiting acetylcholinesterase (AChE) and butyrylcholinesterase enzymes that reduce the hydrolysis of the neurotransmitter acetylcholine, thereby promoting greater cholinergic activity. In the central nervous system, it is AChE rather than butyrylcholinesterase that is primarily involved in synaptic function, and hence AChE provides the main therapeutic target for drug intervention.

Donepezil (E2020; (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one hydrochloride [Aricept, Eisai Co Ltd, Tokyo, Japan]) is a piperidine-based agent that is chemically unique from other cholinesterase inhibitors.[5-8] It is the product of a specific research program designed to produce an agent for the treatment of AD that was highly selective for AChE as opposed to butyrylcholinesterase, reversible in its activity, and that had a pharmacokinetic and pharmacodynamic profile allowing once-daily dosing. Donepezil is a noncompetitive, reversible antagonist of AChE; however, the spectrum of activity against individual isoforms of AChE is unknown. Donepezil is well absorbed, with a relative oral bioavailability of 100%. After oral administration, peak plasma concentrations are achieved within 3 to 4 hours, with an elimination half-life of approximately 70 hours.

The use of donepezil has been shown to improve performance on memory and learning tests in healthy rats, as well as in rats with experimentally induced cholinergic lesions.[9] Preclinical studies[9] indicate that donepezil has greater

Members of the Donepezil Study Group

Future Healthcare Research Centre, Bala Cynwyd, Pa: Milton Alter, MD; *Woodlands Professional Building, Princeton, NJ:* Jeffrey Apter, MD; *Clinical Studies, Peoria, Ariz:* Troy Williams, MD; *NeuroMedical Research Associates, Fort Lauderdale, Fla:* Barry Baumel, MD; *Clinical Studies Ltd, Providence, RI:* Walter Brown, MD; *The Graduate Hospital, Philadelphia, Pa:* Christopher Clark, MD; *Georgetown University Medical Center, Washington, DC:* Stanley Cohan, MD; *Indiana University School of Medicine, Indianapolis:* Martin Farlow, MD; *Clinical Studies, St Petersburg, Fla:* Mildred Farmer, MD; *University of Nebraska Medical Center, Omaha:* David Folks, MD; *Alzheimer's Center, Cleveland, Ohio:* David Geldmacher, MD; *Pharmacology Research Institute, Irvine, Calif:* Jon Heiser, MD; *Community Health Center, Lumberton, NJ:* Claire Jurkowski, MD; *Duke University Medical Center, Durham, NC:* K. Ranga Krishnan, MD; *Thomas Jefferson Medical College, Philadelphia:* Rodney Pelchat, MD, PhD; *West Palm Beach Neurology Group, West Palm Beach, Fla:* Carl Sadowsky, MD; *Columbia University, New York City, NY:* Mary Sano, PhD; *Clinical Studies, Boynton Beach, Fla:* Abbey Strauss, MD; *Wesley Woods Geriatric Hospital, Atlanta, Ga:* Larry Tune, MD; *Geriatric Services, Chicago, Ill:* James Webster, MD; *University of Texas, Dallas:* Myron Weiner, MD; *The Neurology Center, Alexandria, Va:* Stuart Stark, MD.

specificity for brain tissue and is more selective for AChE than either physostigmine or tacrine hydrochloride. In addition, donepezil also has a longer duration of inhibitory action than either of these agents.[7,10] As a consequence of this high selectivity and specificity, donepezil should produce fewer peripheral cholinomimetic-induced adverse effects at effective doses. Indeed, in a phase 2 clinical trial, 5 mg of donepezil hydrochloride was shown not only to provide significant clinical improvements in cognitive and global function in patients with mild to moderately severe AD, but also these benefits were obtained without peripheral cholinergic adverse events, laboratory test abnormalities, or hepatotoxic effects.[11] These findings contrast with those for tacrine; although this agent displays significant efficacy, its clinical use is limited by a high discontinuation rate[12,13] because of dose-limiting adverse effects, including hepatotoxicity.[14]

Inhibition of AChE in red blood cell (RBC) membranes by donepezil has been shown to correspond closely to its effects in the cerebral cortex of rats ($r = 0.94$),[15] with the inhibition in both tissues showing a similar time course—a rapid onset and a linear decline. In addition, a relationship between inhibition of AChE in RBCs and improvement in cognition has been demonstrated in patients with AD.[11] As a consequence, AChE inhibition in RBC membranes has been used as a surrogate marker to model the clinical effectiveness of using donepezil in patients with AD.

The present phase 3 study was undertaken to establish the efficacy and safety of using donepezil in patients with AD, and to define further the relationships between plasma donepezil concentration, inhibition of AChE in RBCs, and clinical response.

Table 1. Patient Characteristics at Baseline

Characteristics	Treatment Group		
	Placebo (n = 153)	Donepezil Hydrochloride, 5 mg/d (n = 157)	Donepezil Hydrochloride, 10 mg/d (n = 158)
Sex, No. (%)			
Male	60 (39)	49 (31)	62 (39)
Female	93 (61)	108 (69)	96 (61)
Age, y			
Mean ± SEM	74.0 ± 0.65	73.8 ± 0.67	73.4 ± 0.65
Range	52-93	50-94	50-92
Weight, kg			
Mean ± SEM	66.05 ± 1.01	65.72 ± 0.98	67.8 ± 1.13
Range	43.6-100.5	40.9-99.5	35.5-105.2
Race, No. (%)			
White	147 (96)	149 (95)	152 (96)
Black	6 (4)	6 (4)	1 (1)
Other	0	2 (1)	5 (3)
Clinical Dementia Rating, No. (%)			
0.5*	2 (1)	1 (1)	3 (2)
1.0	121 (79)	121 (77)	120 (76)
2.0	30 (20)	35 (22)	35 (22)
Mini-Mental State Examination score			
Mean ± SEM	19.80 ± 0.35	19.39 ± 0.39	19.35 ± 0.40
Range	10-26	10-28	18-28

** These patients represented protocol violations and were subsequently discontinued from the study.*

Table 2. Summary of Patient Withdrawals

	Treatment Group, No. (%)		
	Placebo (n = 153)	Donepezil Hydrochloride, 5 mg/d (n = 157)	Donepezil Hydrochloride, 10 mg/d (n = 158)
Total No. of patients withdrawn	11 (7)	16 (10)	29 (18)
Reasons			
Adverse event(s)*	2 (1)	7 (4)	14 (9)
Serious adverse events*	1 (1)	0 (0)	2 (1)
Intercurrent illness	0 (0)	0 (0)	0 (0)
Request of patient or investigator	3 (2)	4 (3)	6 (4)
Medication noncompliance	1 (1)	0 (0)	0 (0)
Protocol violation	2 (1)	3 (2)	4 (3)
Other	2 (1)	2 (1)	3 (2)

** These events were not necessarily treatment emergent.*

RESULTS

The demographic data for the 468 patients randomized to receive treatment are shown in **Table 1**. Patient ages ranged from 50 to 94 years (mean, 73.7 years) and their body weights from 35.5 to 105.2 kg. Sixty-one percent of the patients receiving placebo, 69% of those receiving 5 mg/d of donepezil hydrochloride and 61% of those receiving 10 mg/d of donepezil hydrochloride were women, thus accurately reflecting the percentage of women in the population with AD.[30] The 3 treatment groups were found to be comparable with respect to all demographic characteristics.

Only 8 patients had been previously treated with other cholinesterase inhibitors, 5 of whom had been enrolled in other investigative clinical trials. These regimens, as required by the protocol, were discontinued at least 30 days before entry into this study.

A high percentage of patients completed the trial: 93% of the placebo group and 90% and 82% of the patients treated with 5 mg/d and 10 mg/d of donepezil hydrochloride, respectively. In total, 56 patients (12%) withdrew from the trial prematurely. The 2 most frequent reasons were adverse events (6%) and withdrawal of consent (3%). As shown in **Table 2**, the incidence of adverse event–related withdrawals (not all of which were treatment emergent) was low overall, but higher in the group receiving a dosage of 10 mg/d who had received a rapid, forced titration from 5 mg/d to 10 mg/d after 7 days. The frequency of adverse events was similar among patients receiving placebo or 5 mg/d of donepezil hydrochloride. The most common adverse events leading to discontinuation were nausea and diarrhea, although, in general, these adverse events were rated as mild and in most cases did not lead to discontinuation. In the treatment group receiving 10 mg/d of donepezil hydrochloride, 3.8% and 2% withdrew because of nausea and diarrhea, respectively.

EFFICACY ASSESSMENT

As a consequence of the low discontinuation rate recorded in this trial, the ITT analyses and analyses of the evaluable patient population gave essentially the same results (**Table 3** and **Table 4**). Further discussion of these results will report the more conservative ITT analyses using the end point data set (ITT LOCF). To confirm the appropriateness of end point analyses and to test for potential bias in the LOCF procedure (due to differential dropout rates among the treatment groups), analyses of observed cases were conducted at week 12 (based only on patients with week 12 values). Results were found to be consistent, indicating bias did not exist. Indeed, the majority of the 468 patients randomized to treatment were included in the ITT LOCF analyses with, for example, only 7 patients being excluded from the ADAS-cog assessment because they had no evaluations while receiving treatment.

PRIMARY EFFICACY PARAMETERS

Statistically significant improvements in ADAS-cog scores in patients treated with donepezil were present from the third week of treatment and were sustained throughout the 12-week double-blind treatment period (**Figure 1**). Scores at the end of the 3-week placebo washout had begun to return to baseline values for the donepezil groups, with the placebo group showing a similar rate of decline; however, the improvement in both donepezil groups remained statistically significant ($P<.001$) compared with placebo.

Table 3. Primary Efficacy Variables*

	Outcome Measures					
	Intention-to-Treat Analysis (LOCF)			Fully Evaluable Population		
Assessment/Score	Placebo	Donepezil Hydrochloride, 5 mg/d	Donepezil Hydrochloride, 10 mg/d	Placebo	Donepezil Hydrochloride, 5 mg/d	Donepezil Hydrochloride, 10 mg/d
ADAS-cog	(n = 150)	(n = 156)	(n = 155)	(n = 135)	(n = 139)	(n = 120)
Mean (± SEM)† baseline score	25.3 (0.87)	26.4 (0.92)	26.4 (0.89)	25.0 (0.90)	26.9 (0.99)	27.2 (0.98)
Range	6.0-51.3	5.7-53.3	4.7-56.7	6.0-51.3	5.7-53.3	4.7-56.3
LS mean (± SEM)‡ change at end point§	0.4 (0.43)	−2.1 (0.43)	−2.7 (0.43)	0.4 (0.47)	−2.2 (0.46)	−2.7 (0.50)
P (treatment vs placebo)‖		<.001	<.001		<.001	<.001
95% Confidence intervals		−3.59 to −1.29	−4.22 to −1.92		−3.85 to −1.37	−4.38 to −1.82
Favors		Donepezil	Donepezil		Donepezil	Donepezil
LS mean (± SEM) change at week 15¶	−1.5 (0.47)	−0.7 (0.47)	−1.6 (0.49)	1.7 (0.48)	−0.6 (0.47)	−1.5 (0.50)
CIBIC plus	(n = 150)	(n = 159)	(n = 152)	(n = 135)	(n = 139)	(n = 120)
Mean (± SEM)‡ score at end point§	4.2 (0.07)	3.9 (0.08)	3.8 (0.08)	4.2 (0.08)	3.9 (0.08)	3.8 (0.08)
P (treatment vs placebo)#		.003	.008		.001	.02
95% Confidence intervals		−0.50 to −0.08	−0.55 to −0.13		−0.55 to −0.11	−0.57 to −0.13
Favors		Donepezil	Donepezil		Donepezil	Donepezil
Mean (± SEM)‡ score at week 15¶	4.2 (0.08)	4.0 (0.09)	4.1 (0.09)	4.2 (0.09)	4.0 (0.09)	4.1 (0.10)

** LOCF indicates last observance while receiving treatment was carried forward; ADAS-cog; Alzheimer's Disease Assessment Scale–Cognitive Subscale; CIBIC plus, Clinicians Interview-Based Impression of Change including caregiver information; LS, least squares mean adjusted for baseline covariate; and ellipses, not applicable.*

† Mean baseline score at randomization.

‡ Least significant difference method with baseline as covariate.

§ End point equals week 12 with LOCF.

‖ P values are based on an analysis of covariance model using the Fisher 2-tailed least significant difference procedure for pairwise comparisons.

¶ After 3 weeks, single-blind, placebo washout. Values are based on number at week 15.

 # P values are based on Cochran Mantel-Haenszel test using RIDITS analysis excluding not assessed.

The mean improvement in ADAS-cog scores at end point, adjusted for baseline severity (least squares mean) was significantly greater for the 5-mg (− 2.1; $P<.001$) and 10-mg donepezil hydrochloride groups (− 2.7; $P<.001$) compared with the decline observed in the placebo group (0.4). The drug-placebo differences were 2.5 and 3.1 ADAS-cog units for the 5-mg/d and 10-mg/d groups, respectively. In general, the magnitude of improvement in mean change in ADAS-cog scores for the 10-mg dosage group appeared to be greater than that for the 5-mg dosage group. However, these differences in magnitude did not reach statistical significance at end point ($P = .28$) by analysis of covariance, although this study was not powered to detect such a difference.

Patients receiving donepezil demonstrated improvements in global function, as measured by the CIBIC plus scale, that were superior to those patients receiving placebo. Overall treatment effects were statistically significant at weeks 9 and 12 and at end point ($P\leq.015$). Pairwise comparisons, using the Cochran-Mantel-Haenszel test, between active treatment groups and placebo were statistically significantly different at weeks 9 and 12 and at end point, except for the comparison between placebo vs the 10-mg/d group at week 9 ($P = .098$; **Figure 2**). The improvement in mean CIBIC plus score at end point was slightly greater for the 10-mg (3.8; $P = .008$) vs the 5-mg (3.9; $P = .003$) dosage group ; (Table 3). The drug-placebo differences in mean CIBIC plus scores at end point were 0.3 for the group receiving 5 mg/d of donepezil hydrochloride and 0.4 for the group receiving 10 mg/d of donepezil hydrochloride. The percentages of patients demonstrating clinical improvement at end point (a score of 1, 2, or 3 on the CIBIC plus) were the following: placebo group, 18%; 5 mg/d of donepezil hydrochloride group, 32%; and 10 mg/d of donepezil hydrochloride group, 38%: an approximate doubling for the active drug groups in comparison with placebo.

SECONDARY EFFICACY PARAMETERS

Overall treatment effects indicating improvement (reflected as a positive change score) in MMSE were found at weeks 3 and 12 and at end point ($P\leq.004$, analysis of covariance) for patients receiving donepezil. The 10-mg/d dosage group exhibited significantly greater improvement than the placebo group at weeks 3, 6, and 12 and at end point, while the 5-mg/d dosage group achieved significance at weeks 3 and 12 and at end point. At week 15 (following 3 weeks of placebo washout) the change scores for both the groups receiving 5 mg/d and 10 mg/d of donepezil hydrochloride remained significantly improved (**Figure 3**). The mean drug–placebo differences at end point were 1.0 and 1.3 for the groups receiving 5 mg/d and 10 mg/d of donepezil hydrochloride during the double-blind phase, respectively (Table 4).

All 3 treatment groups exhibited consistent trends for improvement in CDR-SB scores from week 9 onward (**Figure 4**). The overall treatment effect was sta-

Table 4. Secondary Efficacy Variables*

Assessment Score	Outcome Measures: Intention-to-Treat Analysis (LOCF) Placebo	Donepezil Hydrochloride 5 mg/d	Donepezil Hydrochloride 10 mg/d	Fully Evaluable Population Placebo	Donepezil Hydrochloride 5 mg/d	Donepezil Hydrochloride 10 mg/d
MMSE	(n = 150)	(n = 156)	(n = 156)	(n = 135)	(n = 139)	(n = 120)
Mean (± SEM) baseline score†	19.8 (0.35)	19.4 (0.39)	19.3 (0.40)	19.8 (0.37)	19.1 (0.41)	19.1 (0.43)
Range	10-26	10-28	8-28	10-26	10-26	10-26
LS mean (± SEM)‡ change at end point§	-0.04 (0.25)	1.0 (0.25)	1.3 (0.24)	-0.1 (0.27)	1 (0.27)	1.2 (0.29)
P (treatment vs placebo)‖		≤ .004	≤ .001		.01	.004
95% Confidence intervals		0.33 to 1.65	0.65 to 1.97		0.22 to 1.64	0.38 to 1.86
Favors		Donepezil	Donepezil		Donepezil	Donepezil
LS mean (± SEM)‡ change at week 15¶	-0.03 (0.27)	0.7 (0.27)	0.8 (0.28)	-0.02 (0.28)	0.8 (0.27)	0.8 (0.29)
CDR-SB	(n = 150)	(n = 156)	(n = 154)	(n = 135)	(n = 139)	(n = 120)
Mean (± SEM) baseline score†	6.81 (0.18)	6.85 (0.18)	7.18 (0.20)	6.82 (0.20)	6.95 (0.19)	7.22 (0.22)
LS mean (± SEM)‡ change at end point§	0.14 (0.11)	0.10 (0.11)	-0.31 (0.11)	0.09 (0.12)	-0.06 (0.12)	-0.33 (0.13)
P (overall treatment effect)‖		.32 (NS)			.22 (NS)	
95% Confidence intervals		-0.25 to 0.33	-0.46 to 0.12		-0.29 to 0.35	-0.57 to 0.09
Adjusted mean (± SEM)‡ change at week 15¶	0.03 (0.13)	0.03 (0.13)	-0.27 (0.13)	0.07 (0.13)	0.06 (0.13)	-0.26 (0.14)
QoL	(n = 150)	(n = 155)	(n = 156)	(n = 135)	(n = 138)	(n = 120)
Mean (± SEM) baseline score†	289.4 (3.4)	292.3 (3.6)	283.5 (3.5)	290.8 (3.4)	290.1 (3.8)	284.5 (4.0)
LS mean (± SEM)‡ change at end point§	4.0 (2.7)	5.7 (2.7)	4.3 (2.7)	3.6 (2.9)	6.6 (2.9)	3.2 (3.1)
P (treatment vs placebo)‖		.65	.02		.45	≤ .10
95% Confidence intervals		-5.58 to 8.92	-15.55 to -1.07		-4.72 to 10.66	-14.79 to 1.19
Favors			Placebo			
LS mean (± SEM)‡ change at week 15¶	5.6 (2.9)	2.0 (2.8)	-3.9 (3.0)	5.5 (2.9)	3.5 (2.9)	-3.1 (3.0)

** LOCF indicates last observation while receiving treatment was carried forward; MMSE, Mini-Mental State Examination; CDR-SB, Sum of the Boxes of the Clinical Dementia Rating; LS, least squares mean adjusted for baseline covariate; ellipses, not applicable; NS, not significant; and QoL, quality of life.*

† Mean baseline score at randomization.

‡ Least significant difference method with baseline as covariate.

§ End point equals week 12 with LOCF.

‖ P values are based on an analysis of covariance model using the Fisher 2-tailed least significant difference procedure for pairwise comparisons (also used for the overall treatment effect for CDR-SB).

¶ After 3 weeks single-blind placebo washout. Values are based on number at week 15.

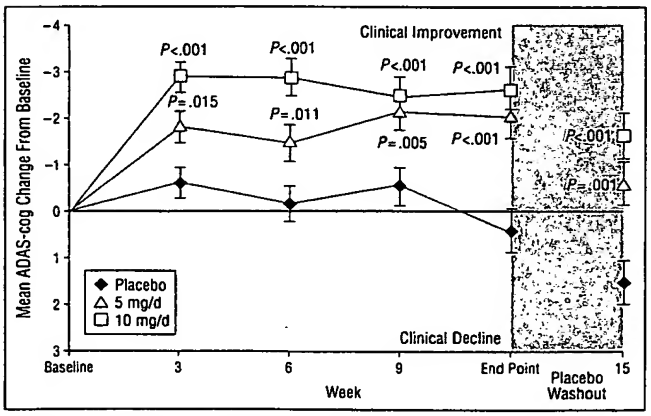

Figure 1. *Least squares mean (± SEM) change from baseline in the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) scores for patients with mild to moderately severe Alzheimer disease receiving 5 mg/d and 10 mg/d of donepezil hydrochloride and placebo. Of the 468 patients randomized to receive treatment, 457 were included in the intention-to-treat analysis at end point.*

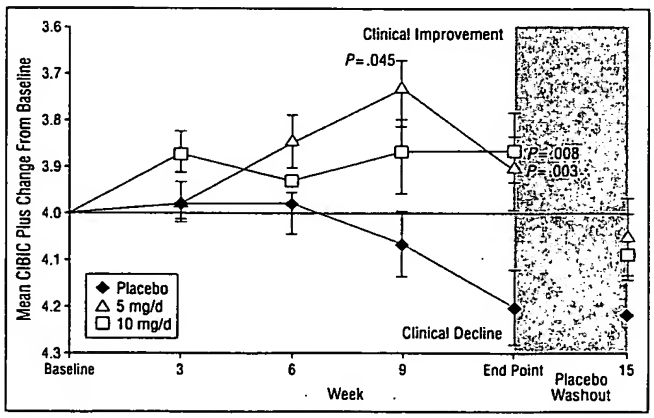

Figure 2. *Mean (± SEM) Clinician's Interview–Based Impression of Change including caregiver information (CIBIC plus) scores for patients with mild to moderately severe Alzheimer disease receiving 5 mg/d and 10 mg/d of donepezil hydrochloride and placebo. Of the 468 patients randomized to receive treatment, 455 were included in the intention-to-treat analysis at end point.*

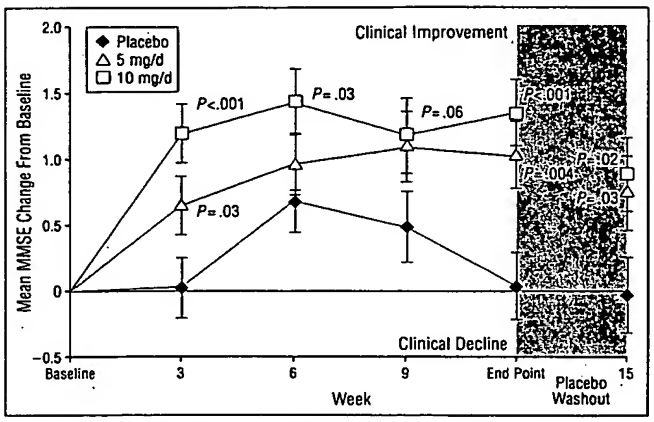

Figure 3. *Least squares mean (± SEM) change from baseline in Mini-Mental State Examination (MMSE) scores for patients with mild to moderately severe Alzheimer disease receiving 5 mg/d and 10 mg/d of donepezil hydrochloride and placebo. Of the 468 patients randomized to receive treatment, 460 were included in the intention-to-treat analysis at end point.*

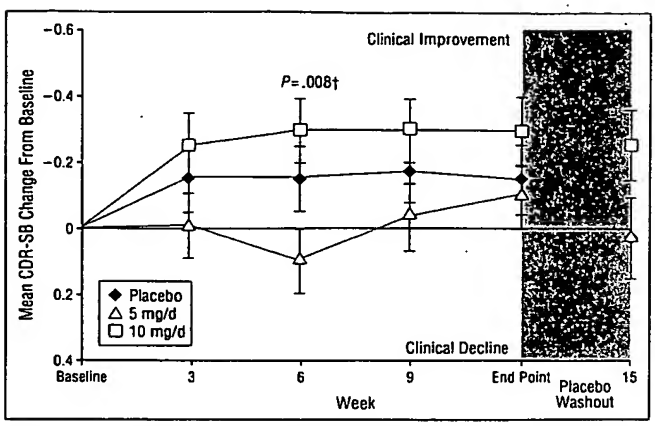

Figure 4. *Least squares mean (± SEM) change from baseline in the Sum of the Boxes of the Clinical Dementia Rating (CDR-SB) scores for patients with mild to moderately severe Alzheimer disease receiving 5 mg/d and 10 mg/d of donepezil hydrochloride and placebo. Of the 468 patients randomized to receive treatment, 459 were included in the intention-to-treat analysis at end point. Dagger indicates overall treatment effect.*

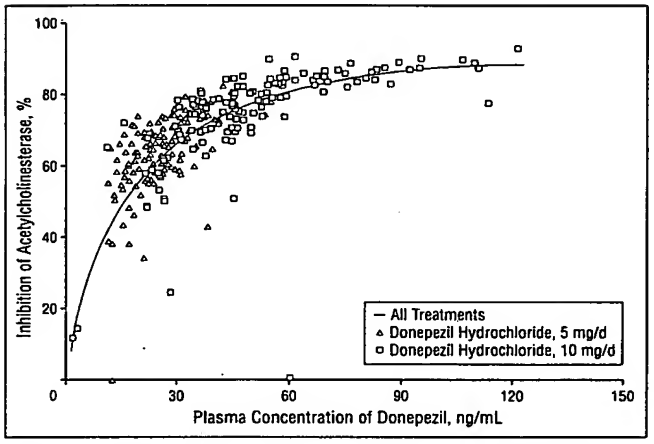

Figure 5. *Correlation between plasma concentrations of donepezil and percentage of acetylcholinesterase inhibition in red blood cells.*

tistically significant at week 6 ($P = .008$); however, pairwise analysis failed to show any significant difference among the treatment groups at any visit (Table 4), even though the mean changes from baseline for the group receiving 10 mg/d of donepezil hydrochloride were lower (showing greatest improvement) than the corresponding placebo values at all visits.

The results from the QoL assessment were highly variable, both between and within patient groups. Overall treatment effects in the ITT sample were statistically significant at week 12 ($P<.05$) and at end point ($P = .02$), with the groups receiving placebo and 5 mg/d of donepezil hydrochloride showing improvement, and the group receiving 10 mg/d of donepezil hydrochloride demonstrating worsening. Results for the fully evaluable population were similar except that there was no significant difference at the end point ($P = .04$).

THERAPEUTIC DRUG MONITORING

The mean (± SEM) donepezil plasma concentrations at study end point were 25.9 ± 0.7 ng/mL (n = 142) and 50.6 ± 1.9 ng/mL (n = 139) in the 5-mg/d and 10-mg/d dosage groups, respectively. Corresponding mean (± SEM) percentages of inhibition of AChE in RBCs were 63.9% ± 0.9% (n = 142) and 74.7% ± 1.2% (n=139) for the 2 donepezil groups, respectively. The relationship between plasma concentrations of donepezil and percentage of AChE inhibition is shown in **Figure 5**. A plateau of inhibition was reached at plasma concentrations higher than 50 ng/mL, and corresponded to 80% to 90% enzyme inhibition. The E_{max} for AChE inhibition in RBCs was 100.8% and the EC_{50} was 15.6 ng/mL.

Correlations between plasma concentrations of donepezil and changes in ADAS-cog ($P<.001$) and CIBIC plus ($P = .006$) were statistically significant, as was the correlation between AChE inhibition and change in ADAS-cog ($P<.001$) and CIBIC plus ($P = .005$).

SAFETY

Donepezil was generally well tolerated. As expected in an elderly population, a high number of adverse events were reported for both the drug-treated and placebo-treated groups. The incidences of TESS for both dosages of donepezil hydrochloride (68% at 5 mg/d and 78% at 10 mg/d) were comparable with the incidences observed with placebo (69%). In the majority of cases (92%) these TESS were judged to be mild.

As shown in **Table 5**, the only adverse events significantly more common with donepezil use were nausea, insomnia, and diarrhea ($P<.001$), which also appeared to be dose related. These are the types of adverse events expected from treatment with AChE inhibitors. Many events were mild and transient (lasting 1 or 2 days), and resolved with continued donepezil treatment without the need for adjunct antidiarrheal and/or antiemetic treatment.

Seven patients treated with placebo and 6 in each of the donepezil groups suffered serious adverse events during the trial. Three patients had events that were considered possibly related to treatment with donepezil. These included stomach ulcer with hemorrhage (5 mg/d); syncope and transient ischemic attack (5 mg/d); and nau-

Table 5. Summary of Treatment-Emergent Signs and Symptoms (TESS)*

Preferred Term‡	No. (%) of Patients With TESS†, Treatment Group: Placebo (n = 153)	Donepezil Hydrochloride 5 mg/d (n = 157)	Donepezil Hydrochloride 10 mg/d (n = 158)	P§
No. of patients with ≥1 TESS	106 (69)	106 (68)	124 (78)	
Nausea	12 (8)	11 (7)	34 (22)	<.001‖
Insomnia	8 (5)	13 (8)	28 (18)	.001‖
Diarrhea	4 (3)	10 (6)	21 (13)	.001‖
Pain	11 (7)	14 (9)	21 (13)	.20
Headache	13 (8)	21 (13)	19 (12)	.37
Dizziness	10 (7)	14 (9)	14 (9)	.69
Muscle cramp	6 (4)	9 (6)	12 (8)	.37
Fatigue	8 (5)	5 (3)	12 (8)	.22
Accident	11 (7)	9 (6)	10 (6)	.87
Agitation	11 (7)	7 (4)	10 (6)	.59
Vomiting	7 (5)	5 (3)	10 (6)	.41
Anorexia	4 (3)	6 (4)	10 (6)	
Weight loss	3 (2)	3 (2)	8 (5)	
Common cold	10 (7)	8 (5)	7 (4)	.69
Abdominal disturbance	6 (4)	9 (6)	6 (4)	
Urinary tract infection	20 (13)	10 (6)	6 (4)	.009¶
Stomach upset	1 (1)	8 (5)	5 (3)	
Rhinitis	6 (4)	8 (5)	5 (3)	
Upper respiratory tract infection	6 (4)	8 (5)	5 (3)	
Edema in extremities	8 (5)	1 (1)	4 (3)	
Cough	8 (5)	2 (1)	3 (2)	

*Ellipses indicate not applicable.
†Incidence of TESS of 5% or more in any randomized group.
‡Derived from COSTART dictionary.[28]
§P value comparing the 3 treatment groups using Fisher exact tests.
‖More frequent with the use of donepezil.
¶More frequent with placebo.

sea, aphasia, tremor, and diaphoresis (10 mg/d). One patient in the placebo group died as a result of renal failure.

Both groups of patients treated with donepezil had group mean decreases in heart rate relative to baseline (mean, 2.65/min in the 5-mg/d group and 2.26/min in the 10-mg/d group). These reductions were significantly larger than those observed in the placebo group (0.09/min reduction; $P<.03$). However, the incidence of bradycardia in individual patients (heart rate <50/min) was not significantly different among the treatment groups. These changes in mean group heart rate are considered small and clinically unimportant.

Two patients treated with donepezil hydrochloride, both in the 5-mg/d dosage group, had notable electrocardiographic changes. One patient developed varying degrees of intraventricular conduction defect and premature ventricular contractions; however, this patient exhibited nonspecific ST abnormalities at screening. The other patient was reported to have sinus arrhythmia, left axis deviation, and increased QRS voltage possibly secondary to left ventricular enlargement. Neither patient reported cardiovascular adverse events. Two patients in the placebo group had abnormalities shown on the electrocardiograms: one with left bundle-branch block, the other with sinus bradycardia with premature ventricular contractions.

There were no clinically significant treatment-related effects on vital signs, hematologic examination findings or clinical biochemistry test results. More important, the use of donepezil was not associated with any hepatotoxic effects.

COMMENT

The results reported herein demonstrate that once-daily administration of donepezil enhances cognition, measured by standardized psychometric testing, and improves clinician-rated global function, measured by CIBIC plus, in patients with mild to moderately severe AD. The cognitive improvements began during the initial 3 weeks of treatment, and by the first visit during the double-blind phase the improvements measured by ADAS-cog were maximal and statistically significant (Figure 1). This improvement was sustained throughout the study. At end point (week 12 LOCF, the end of the double-blind phase), the adjusted mean treatment effect of donepezil hydrochloride relative to placebo was 2.5 points at the 5-mg/d dosage, and 3.1 points at the 10-mg/d dosage, with a higher proportion of the patients receiving 10 mg/d having the larger reductions in ADAS-cog scores. During the 3-week placebo washout phase, scores demonstrated a trend toward a return to baseline values, although the treatment effect at week 15 remained statistically significant ($P<.001$) relative to baseline for the groups receiving 5 mg/d and 10 mg/d of donepezil hydrochloride. In contrast, no significant effect was seen for the placebo group.

During the 12-week active treatment period, approximately 60% of patients receiving 10 mg/d of donepezil achieved a best change score of 4 points or more on the ADAS-cog, as opposed to approximately 30% of the placebo controls. An improvement of 4 or more points on the ADAS-cog is considered by regulatory authorities to be clinically meaningful. The withdrawal rate was 7% in the placebo group, 10% in the 5-mg/d dosage group, and 18% in the 10-mg/d dosage group. A conservative measure, adjusting for these withdrawals (ITT analysis), shows that between 48% and 57% of patients randomized to receive drug treatment achieved a 4-point or more reduction in ADAS-cog compared with 29% for placebo. These data are consistent with a 24-week study that showed a greater effect on ADAS-cog with 10 mg/d than with 5 mg/d of donepezil hydrochloride.[31] These improvements in ADAS-cog were accompanied by mean drug–placebo differences at end point in MMSE scores of 1.0 and 1.3 for the groups receiving 5 mg/d and 10 mg/d of donepezil hydrochloride, respectively. In general, the magnitude of improvement in mean change in ADAS-cog and MMSE scores appeared to be greater for the group receiving 10 mg/d than for the group receiving 5 mg/d of donepezil hydrochloride, although the results did not reach statistical significance.

It should be mentioned that the ADAS-cog, although one of the most recognized and widely used scales for the measurement of cognitive function, lacks linearity and possesses floor and ceiling effects. Thus, the rate of disease progression, when expressed as point increases in ADAS-cog per year, for patients with mild (floor) and severe (ceiling) dementia appears slower than that for patients with moderate dementia. This difference represents a limitation in the ability of the tool to discriminate changes in cognitive capabilities at the mild and severe ends of the spectrum of disease, rather than any true differences in the rate of progression of neuropathologic conditions. Due to this limitation, effect sizes in populations dominated by patients with mild or severe dementia whose annualized rate of decline may be 5 points or lower (baseline ADAS-cog scores of 15, mild; and of 55, severe) will appear numerically smaller than those from a population dominated by patients with moderate dementia whose annualized rate of decline may be as much as 12 or more points (baseline ADAS-cog score of 35). The range normally reported for untreated patients with moderate disease is between 7 and 11 points per year.[32,33] Hence, when examining treatment effect sizes between and within clinical studies, it is essential that effect size as a proportion of the annualized rate of change in the placebo cohort be considered. In this study, the mean baseline ADAS-cog score was 26 and approximately 80% of patients had a CDR rating score of 1.0, indicating a population dominated by patients with mild dementia.

Improvements in CIBIC plus scores were also observed in patients treated with donepezil. Although not apparent until week 9, the donepezil hydrochloride groups were rated higher than the placebo group (3.9 for the 5-mg/d group, 3.8 for 10-mg/d group vs 4.2 for the placebo group) at end point, and this difference failed to dissipate completely after donepezil use was discontinued during the 3-week washout period. There was no statistically significant improvement ($P>.05$) in CDR-SB scores, probably because of the short duration of the study. Nonetheless, a trend for improvement was clearly and consistently evident. However, attempts at QoL measurement were unsuccessful in this study, and it is unclear why no treatment effect was observed. These results are inconsistent with those obtained in a 24-week pivotal trial in which the use of donepezil hydrochloride (5 and 10 mg/d) showed trends for improvement in QoL assessment.[31]

Plasma concentrations of donepezil were directly related to AChE inhibition in RBCs (Figure 5) and to improvements in cognitive and global function (ADAS-cog and CIBIC plus). There was also a statistically significant correlation between inhibition of AChE in RBCs and improvement in ADAS-cog ($P<.001$) and CIBIC plus ($P<.005$) scores. Other researchers have described an inverted U-shaped dose response curve for drugs such as physostigmine and metrifonate, reporting that maximum clinical efficacy corresponded to 40% cholinesterase inhibition (plasma butyrylcholinesterase measurements).[34,35] In our study, 50% inhibition of AChE in RBCs was seen at a plasma donepezil concentration of 15.6 ng/mL, and a plateau of enzyme inhibition (80%-90%) was attained at higher plasma concentrations. Statistically significant improvement in ADAS-cog scores was correlated with AChE inhibition in RBCs of 65% or more as opposed to the 40% inhibition value for plasma cholinesterase that has been reported for the other agents. There appears to be a close relationship between percentage of inhibition and drug effect for donepezil.

The rate of patient withdrawal from treatment was much lower with the use of donepezil than with the rates reported for other cholinesterase inhibitors, such as physostigmine, rivastigmine (ENA-713), velnacrine maleate, and tacrine.[12,36-38] All these cholinesterase inhibitors are associated with a higher incidence of peripheral cholinergic adverse effects than the use of donepezil, with some (tacrine and velnacrine) being associated with hepatotoxic effects.[12,36-38] One of several factors contributing to this low rate of patient withdrawal is that the long half-life of donepezil (approximately 70 hours) combined with the once-daily administration produced AChE inhibition with little diurnal variation and a slow and gradual rise to steady state levels of activity. Once-daily dosage also aids medication compliance. Indeed, 95% of patients were more than 80% compliant at each postbaseline visit during the treatment phase of the study.

Analysis of the reported incidences of TESS and treatment-emergent laboratory abnormalities demonstrated that donepezil is well tolerated. There were no unexpected adverse events, and TESS observed were consistent with those reported in other donepezil clinical trials of 12- and 24-week durations.[11,31] The only dose-related adverse events in this study were anticipated cholinergic effects, including mild nausea, diarrhea, and insomnia, which occurred primarily in the group receiving 10 mg/d of donepezil hydrochloride at the time of the forced dosage increase from 5 mg/d to 10 mg/d. These events were generally self-limiting, resolving in 1 to 2 days without the need for interruption or adjustment of the donepezil dosage. Subsequent analysis from an open-label extension study of the use of donepezil in 269 patients who had received placebo in the double-blind pivotal trial phase demonstrated that the occurrence of these

events is minimized when a longer dosage titration period is used. When these patients entered into the open-label extension study, escalation to 10 mg/d of donepezil hydrochloride was undertaken after 4 to 6 weeks at 5 mg/d. As a consequence, the incidence of these adverse events was reduced and was comparable with that experienced with both 5 mg/d of donepezil hydrochloride and placebo. Donepezil produced no statistically significant treatment-emergent laboratory abnormalities, including liver function tests.

The results of this study indicate that donepezil is a well-tolerated and efficacious agent for the symptomatic treatment of mild to moderately severe AD. Statistically significant improvements in scores on tests of cognition are present as early as 3 weeks after starting treatment with donepezil, and statistically significant global improvement was observed after 9 to 12 weeks. Based on ADAS-cog and CIBIC plus results, clinicians should recognize significant improvement in cognitive and global functioning in about 35% to 60% of patients with AD treated with donepezil, while observing stabilization of cognitive function (compared with the decline typically observed in untreated patients) in an additional 20% to 45%. Thus, improvement of cognitive function, or no change in cognitive function, is likely to be seen in approximately 80% of patients with AD treated with donepezil. Further studies are needed to define the role of donepezil in treating patients more severely affected with AD and to determine its long-term efficacy and tolerability.

Accepted for publication November 20, 1997.

From Eisai Inc, Teaneck, NJ (Drs Rogers and Friedhoff); Baylor College of Medicine, Houston, Tex (Dr Doody); and the Department of Psychiatry, Mount Sinai Medical Center, New York, NY (Dr Mohs).

This study was supported by Eisai Inc, Teaneck, NJ, and Eisai Co Ltd, Tokyo, Japan.

Reprints: Medical Communications, Eisai Inc, Glenpointe Centre West, 500 Frank W. Burr Blvd, Teaneck, NJ 07666-6741.

REFERENCES

1. Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry.* 6th ed. Baltimore, Md: Williams & Wilkins; 1995:2562.
2. Giacobini E. Pharmacotherapy of Alzheimer disease: new drugs and novel strategies. *Prog Brain Res.* 1993;98:447-454.
3. Davis RE, Doyle PD, Carroll RT, Emmerling MR, Jaen J. Cholinergic therapies for Alzheimer's disease. *Arzneimittelforschung Drug Res.* 1995;45:425-431.
4. Davis P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet.* 1976;2:1403.
5. Cardozo MG, Iimura Y, Sugimoto H, Yamanishi Y, Hopfinger AJ. QSAR analysis of the substituted inanone and benzylpiperidine rings of a series of indanone-benzylpiperidine inhibitors of acetylcholinesterase. *J Med Chem.* 1992;35:584-589.
6. Cardozo MG, Kawai T, Iimura Y, Sugimoto H, Yamanishi Y, Hopfinger AJ. Conformational analysis and molecular shape comparisons of a series of indanone-benzylpiperidine inhibitors of acetylcholinesterase. *J Med Chem.* 1992;35:590-601.
7. Sugimoto H, Iimura Y, Yamanishi Y, Yamatsu K. Synthesis and anti-cholinesterase activity of 1-benzyl-4-[(5,6-dimethoxy-l-indanone-2-yl) methyl] piperidine hydrochloride (E2020) and related compounds. *Bioorg Med Chem Lett.* 1992;2:871-876.
8. Sugimoto H, Tsuchiya Y, Sugumi H, et al. Novel piperidine derivatives: synthesis and anti-cholinesterase activity of 1-benzyl-4-[2-(N-benzoylamino)ethyl] piperidine derivatives. *J Med Chem.* 1990;33:1880-1887.
9. Rogers SL, Yamansihi Y, Yamatsu K. E2020: the pharmacology of a piperidine cholinesterase inhibitor. In: Becker R, Giacobini E, eds. *Cholinergic Basis for Alzheimer Therapy.* Boston, Mass: Birkhäuser; 1991:314-320.
10. Sugimoto H, Tsuchiya Y, Sugumi H, et al. Synthesis and structure activity relationships of acetylcholinesterase inhibitors of 1-benzyl-4-(2-phthalimidoethyl) piperidine and related derivatives. *J Med Chem.* 1992;35:4542-4548.
11. Rogers SL, Friedhoff LT, and the Donepezil Study Group. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicenter, randomized, double-blind, placebo-controlled trial. *Dementia.* 1996;7:293-303.
12. Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Garcon SI, for the Tacrine Study Group. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. *JAMA.* 1994;271:985-991.
13. Farlow M, Garcon SI, Hershey LA, Lewis KW, Sadowsky CH, Dolan-Ureno J. A controlled trial of tacrine in Alzheimer's disease. *JAMA.* 1992;268:2523-2529.
14. Taylor P. Anticholinesterase agents. In: Gilman AG, Rall TW, Nies AS, Taylor P, eds. *Goodman and Gilman's the Pharmacological Basis of Therapeutics.* 8th ed. New York, NY: McGraw-Hill Book Co; 1993:131-149.
15. Sherman K. Pharmacodynamics of oral E2020 and tacrine in humans: novel approaches. In: Becker R, Giacobini E, eds. *Cholinergic Basis for Alzheimer Therapy.* Boston, Mass: Birkhäuser; 1991:321-328.
16. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34:939-944.
17. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition.* Washington, DC: American Psychiatric Association; 1987.
18. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of subjects for the clinician. *J Psychiatr Res.* 1975; 12:189-198.
19. Hughes CD, Berg L, Danziger L, Coben LA, Martin RL. A new rating scale for the staging of dementia. *Br J Psychiatry.* 1982;140:566-572.
20. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry.* 1984;141:1356-1364.
21. Schneider LS, Olin JT, Doody RS, et al, and the Alzheimer's Disease Cooperative Study. Validity and reliability of the Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change. *Alzheimer Dis Assoc Disord.* 1997;11 (suppl 2):S22-S32.
22. Berg L, Miller JP, Baty J, Rubin EH, Morris JC, Figiel G. Mild senile dementia of the Alzheimer type: 4 evaluations of intervention. *Ann Neurol.* 1992;31: 242-249.
23. Blau TH. Quality of life, social indicators and criteria of change. *Prof Psychol.* 1977;8:464-473.
24. Lee JW, Rogers SL, Friedhoff LT, Cooper NM. Validation and application of an HPLC method for the determination of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine HCl (E2020) in human plasma. *Pharm Res.* 1992;9:S350.
25. Hulse JD, Rogers SL, Friedhoff LT, Sukovaty R, Pedersen JE, Lee JW. A radioenzyme assay of acetylcholinesterase activity in red blood cells and its correlation with 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine HCl. *Pharm Res.* 1992;9:S228.
26. Neter J, Wasserman W, Kutner M. *Applied Linear Statistical Models.* Homewood, Ill: Richard D Irwin Inc; 1990.
27. Cochran WG. Some methods for strengthening the common χ^2 tests. *Biometrics.* 1954;10:417-451.
28. Bross IDJ. How to use RIDIT analysis. *Biometrics.* 1958;14:18-38.
29. US Food and Drug Administration, Center for Drug Evaluation and Research, Office of Epidemiology and Biostatistics. *COSTART: Coding Symbols for Thesaurus of Adverse Reaction Terms.* 4th ed. Washington, DC: US Food and Drug Administration; 1993. Publication PB93-209138.
30. Bachman DL, Wolf PA, Linn R, et al. Prevalence of dementia and probable senile dementia of the Alzheimer's type in the Framingham Study. *Neurology.* 1992; 42:115-119.
31. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT, and the Donepezil Study Group. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology.* 1998;50:136-145.
32. Stern RG, Mohs RC, Davidson M, Schmeidler J, Silverman J, Kramer-Ginsberg E. A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. *Am J Psychiatry.* 1994;151:390-396.
33. Kramer-Ginsberg E, Mohs RC, Aryan M, et al. Clinical predictors of the course of Alzheimer's disease patients in a longitudinal study: a preliminary report. *Psychopharmacol Bull.* 1988;24:458-462.
34. Thal LJ, Maasur DM, Fuld PA, Sharpless NS, Davies P. Memory improvement with oral physostigmine and lecithin in Alzheimer's disease. In: Katzman R, ed. *Banbury Report: Biological Aspects of Alzheimer's Disease.* 9th ed. New Haven, Conn: Cold Spring Harbor Laboratory; 1983;15:461-470.
35. Becker R, Colliver J, Elble R, et al. Effects of metrifonate, a long acting cholinesterase inhibitor in Alzheimer's disease: report of an open trial. *Drug Dev Res.* 1990;19:425-434.
36. Antouno PG; for the Mentane Study Group. Effectiveness and safety of velnacrine for the treatment of Alzheimer's disease: a double-blind, placebo-controlled study. *Arch Intern Med.* 1995;155:1766-1772.
37. Harrell LE, Jope RS, Falgout J, et al. Biological and neuropsychological characterization of physostigmine responders and nonresponders in Alzheimer's disease. *J Am Geriatr Soc.* 1990;38:113-122.
38. Anand R, Gharabawi G, Enz A. Efficacy and safety results of the early phase studies with Exelon (ENA-713) in Alzheimer's disease: an overview. *J Drug Dev Clin Pract.* 1996;8:1-8.

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☑ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.